vol 17 no 9 SEPTEMBER 60

American Journal of Hospital Pharmacy

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American Journal of Hospital Pharmacy

American Society of Hospital Pharmacists

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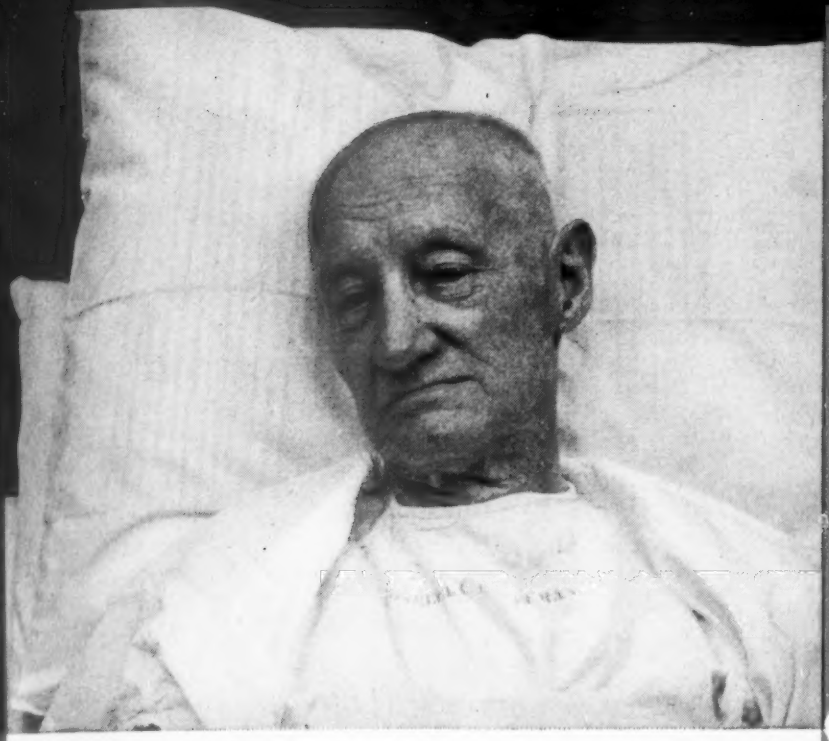

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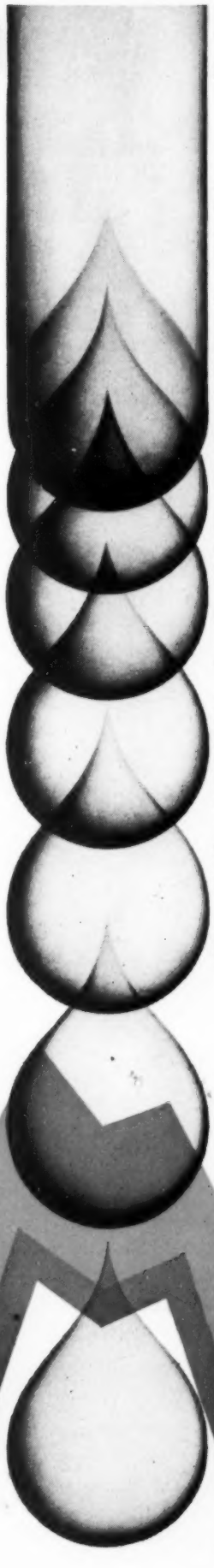

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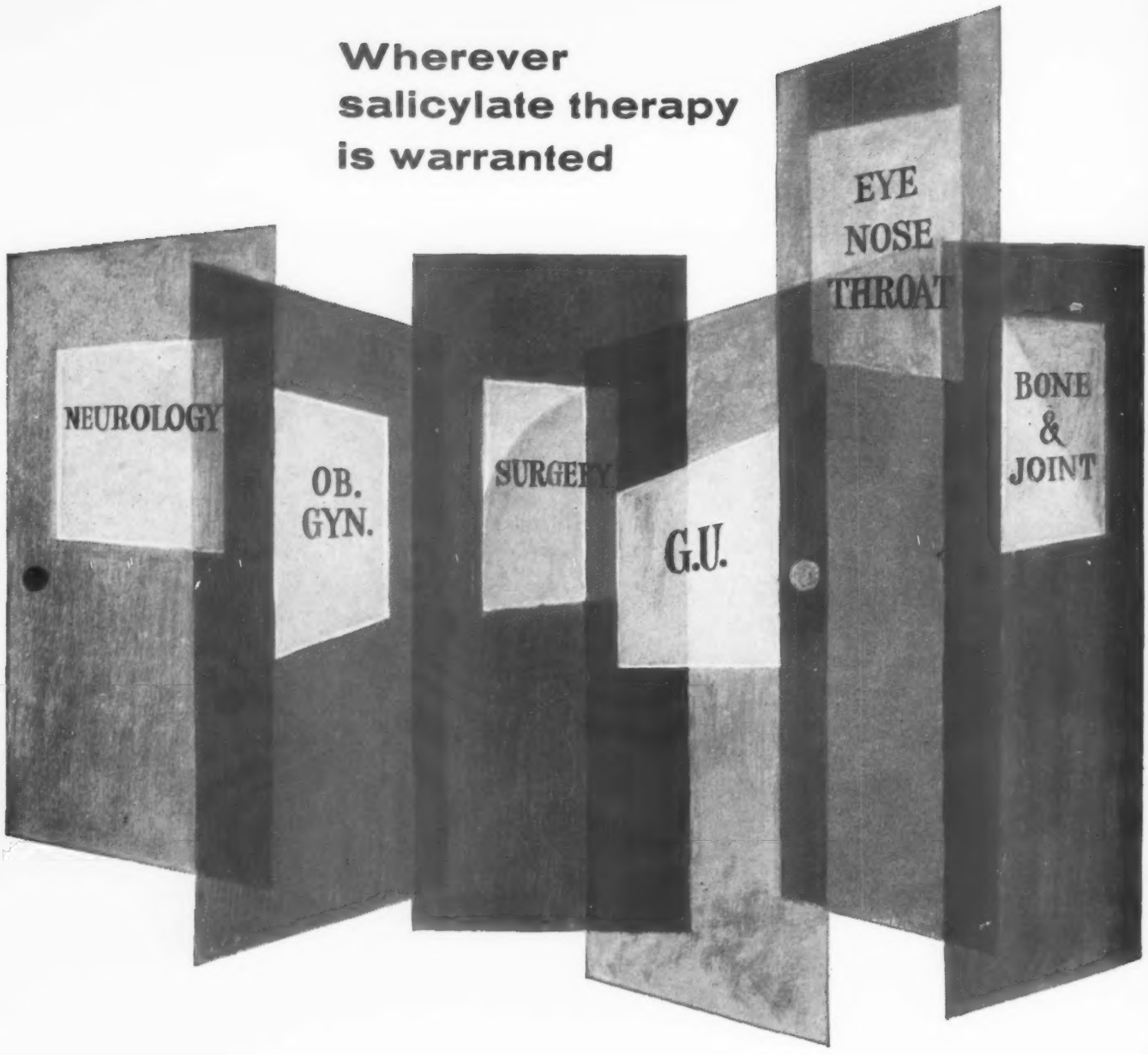

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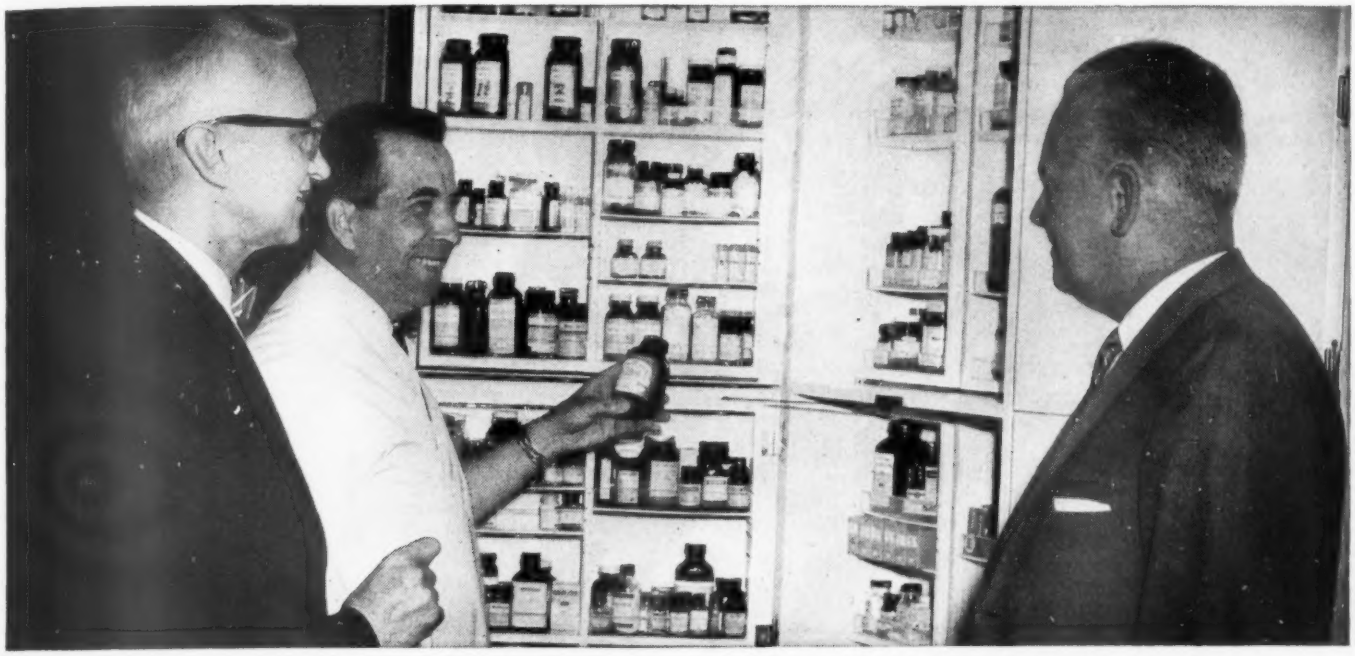

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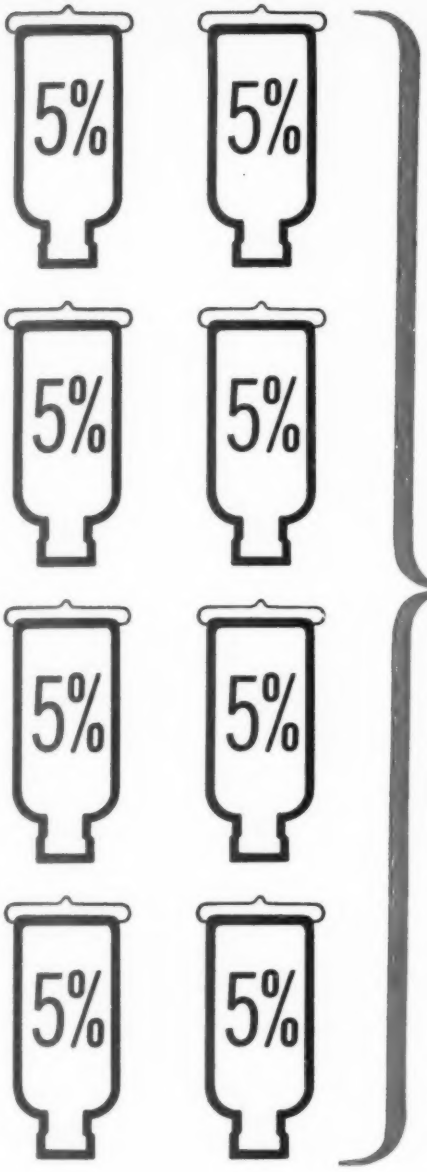

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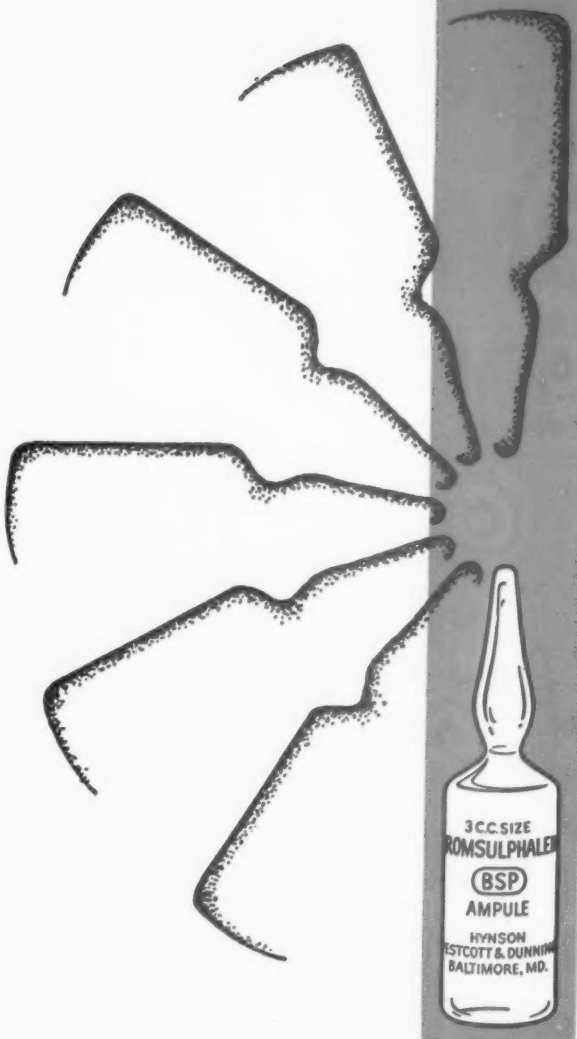

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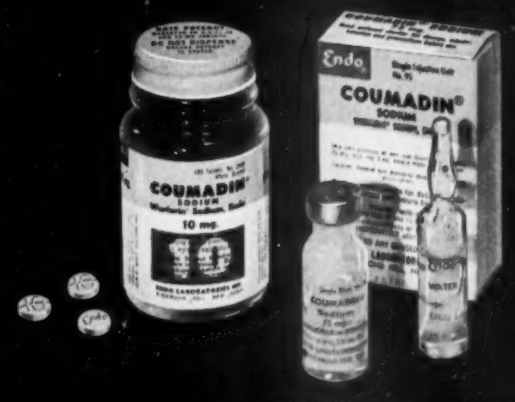

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1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

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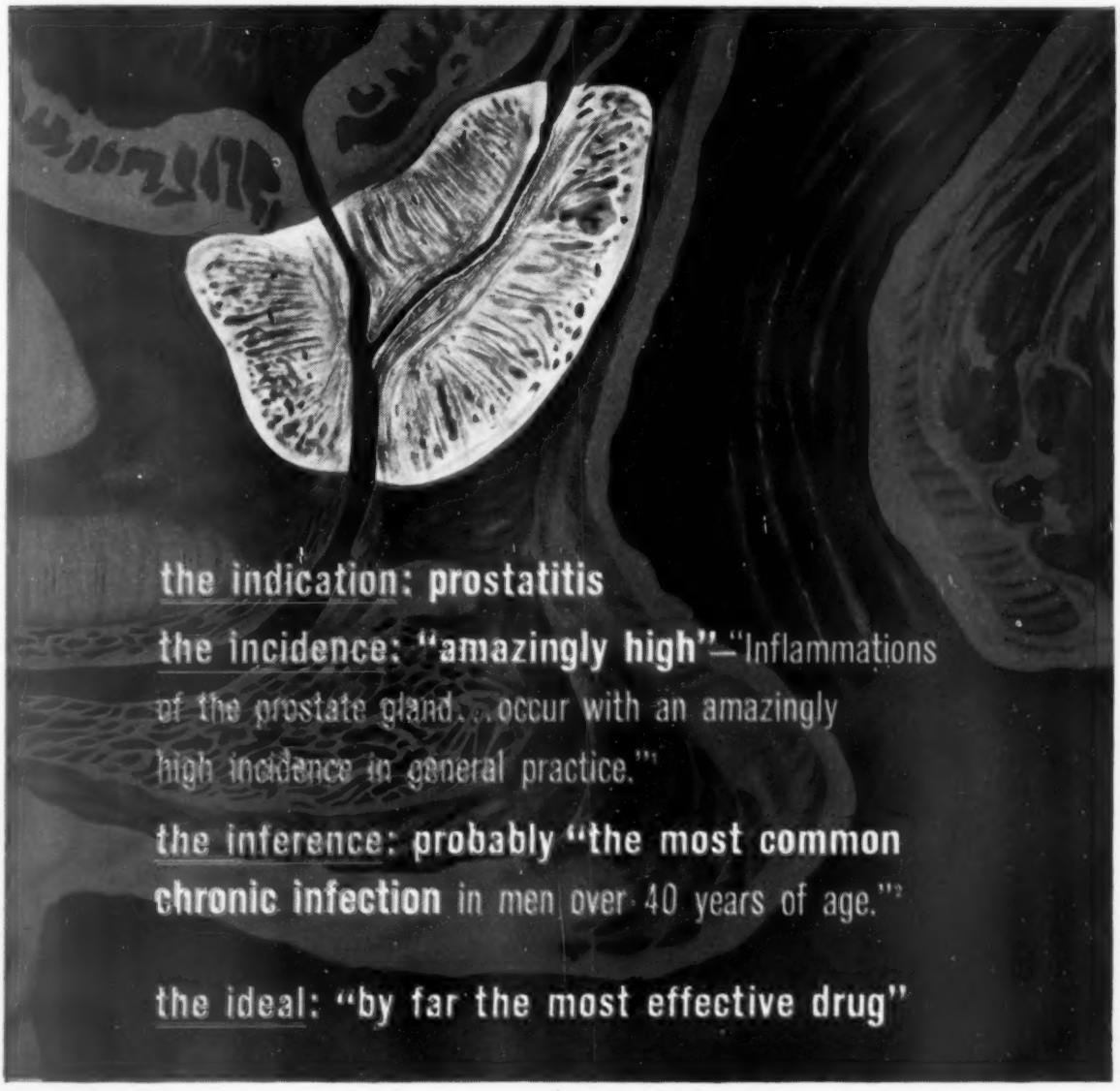

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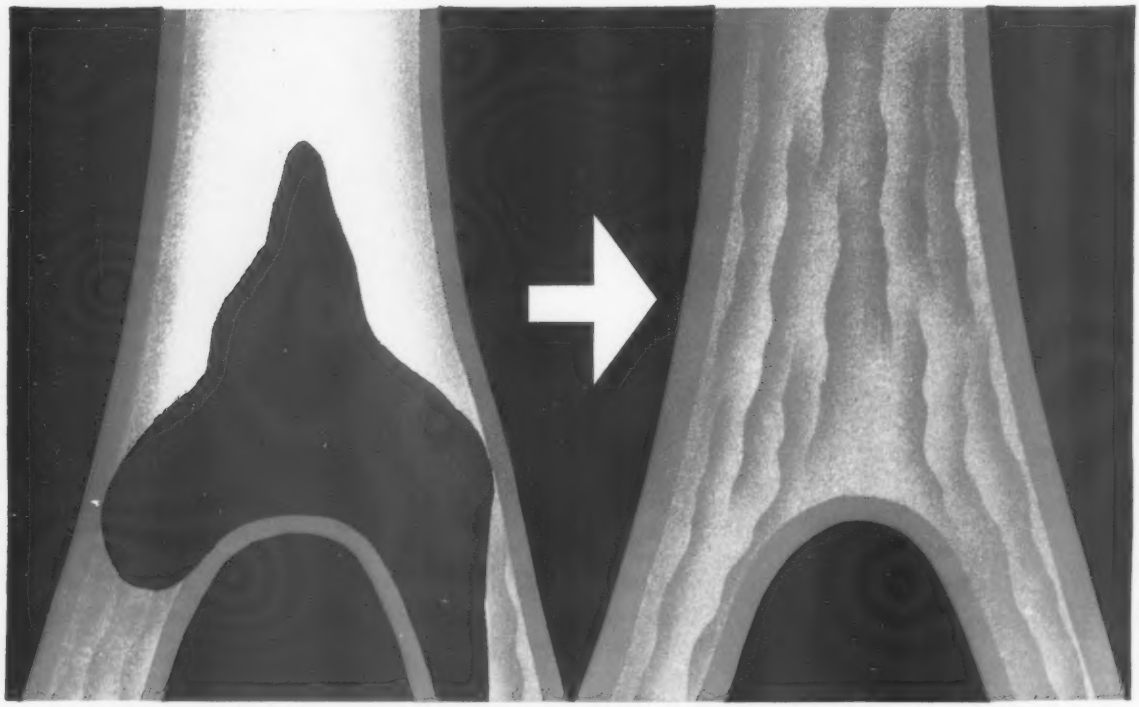

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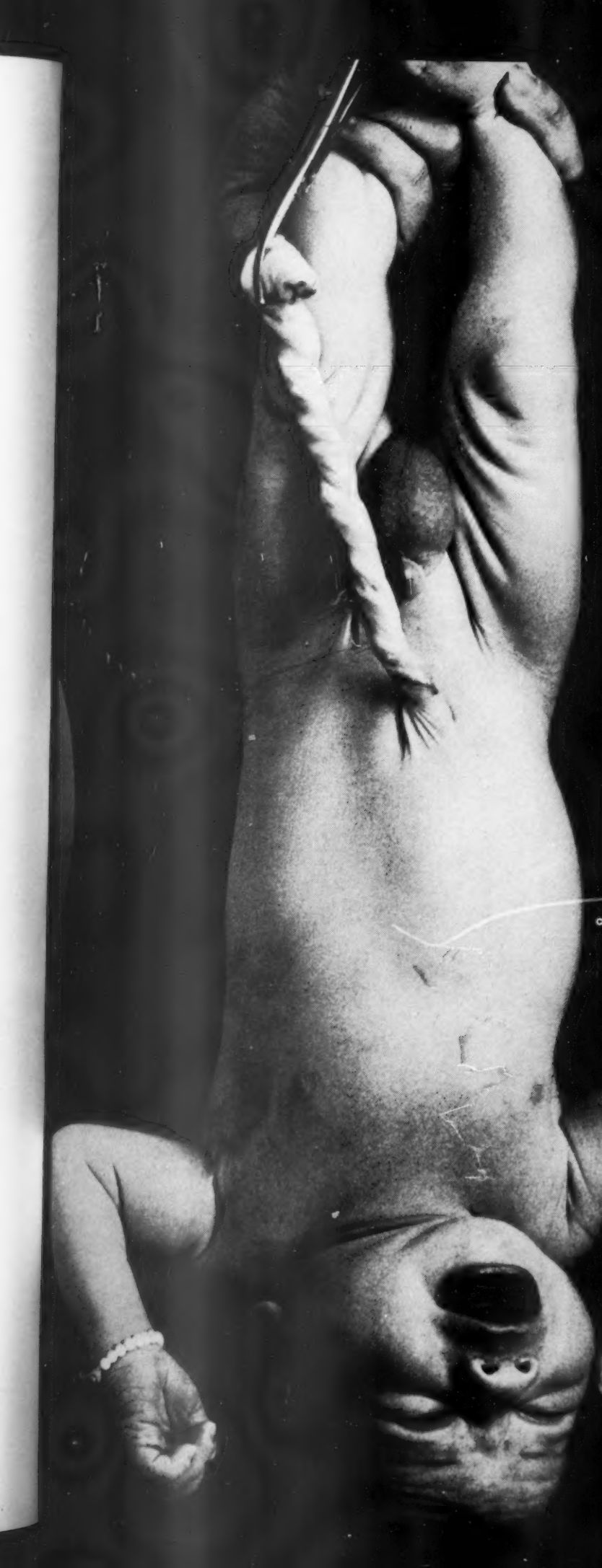

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Lewandowski, Leon A., 212 7th Ave., W., Ashland

Journal Binders Available

A loose-leaf binder for the AMERICAN JOURNAL OF HOSPITAL PHARMACY is now available from The Hamilton Press, Hamilton, Illinois. The new binder has been designed for THE JOURNAL and will hold the twelve issues satisfactorily. The binder is brown in color and "American Journal of Hospital Pharmacy" is embossed on it in gold. The binder is 9 by 12¼ inches with the spine measuring 4 inches.

The cost of the binder is four dollars ($4.00) each and orders may be directed to The Hamilton Press, Hamilton, Illinois.

Lehn & Fink
PROFESSIONAL DIVISION

staph newsletter

EIGHTH OF A SERIES WITH SIGNIFICANT SUGGESTIONS FOR CONTROLLING CROSS INFECTION

MORE and more each month as everyone—those in the hospital as well as others of us concerned with infection control—learns more about the continuing importance of the problem, we seem to be getting an increasing number of requests for specific instructions on not only "how to" but "how frequently" disinfectants should be applied. Fortunately, the simplicity of applying Amphyl®, O-syl®, or Lysol® disinfectants, and Tergisyl® detergent-disinfectant, makes it possible for us to furnish you with easy-to-follow instructions on any one of them. The frequency with which they need to be used in various applications, however, may vary widely depending upon the degree of environmental contamination to which the particular area is exposed. Many hospitals have done their own bacteriological testing and set up their own standards of frequency on various services. For general guidance, you may find the following suggestions helpful.

Writing on "Sanitation in Patient Care Areas", Dr. Ruth B. Kundsin (Journal of the American Medical Women's Association, January, 1960) emphasizes the dangers of bacterial fall-out from commonplace hospital activities and suggests two methods of attack: 1) to decrease fall-out by a careful re-evaluation of activities, and 2) to destroy bacteria deposited. Among the recommendations made to accomplish the latter is disinfection of floors by the wet pickup technic on the following schedule: "daily disinfection—corridors, delivery room, dressing room, emergency ward, isolation rooms, nursery, pediatric ward, and utility rooms; weekly disinfection—medical ward and surgical ward; and terminal disinfection—autopsy room, single room, maternity ward, and operating room."

Dr. H. Taylor Caswell and his co-workers at the 900-bed Temple University Medical Center reveal some interesting figures on both the incidence and control of staphylococcal infections as experienced over three years with 60,000 admissions a year. (Surgery, Gynecology & Obstetrics, May, 1960) While infection in 10,000 clean surgical wounds each year decreased approximately 60%, there was an appreciable increase in hospital related medical infections with phage type 80/81 identified in 71%. Concurrently, the number of patients admitted for treatment of staphylococcal disease doubled—emphasizing the hospital's problem in care of this constant flow of heavily contaminated patients into the hospital from the community.

May we again mention that one of the best dramatizations of how the staph-infected patient can contaminate the hospital is shown in the color motion picture, "Hospital Sepsis: A Communicable Disease", sponsored jointly by the AHA, AMA, and ACS on an industry grant with technical supervision by Dr. Carl W. Walter? When this film is shown in your hospital, be sure to see it. An essential measure recommended to control spread of staph through the environment is generous use of bactericidal cleaning methods.

L & F's Tergisyl® detergent-disinfectant fits the recommendations made by Dr. Walter when describing his floor-flooding technic at a Massachusetts Medical Society meeting—that a synthetic phenolic is the product of choice for operating room floor care. We have just revised our 24-page booklet on Tergisyl and would be glad to send you a copy, or as many copies as you would like for teaching purposes. Included are suggestions for use of this combined cleaning and disinfecting agent in all areas of the hospital in the economical new 1:100 dilution. Tergisyl is also the detergent-disinfectant used at Huggins Hospital in Wolfeboro, New Hampshire, under Dr. Ralph Adams' instructions, to achieve "near sterility" of operating room floors, walls, and furniture following his "zone concept" of bacteriologic cleanliness. (SG&O, March, 1960) If you would like this new booklet, a reprint of Dr. Adams' article, and Tergisyl samples, please write us.

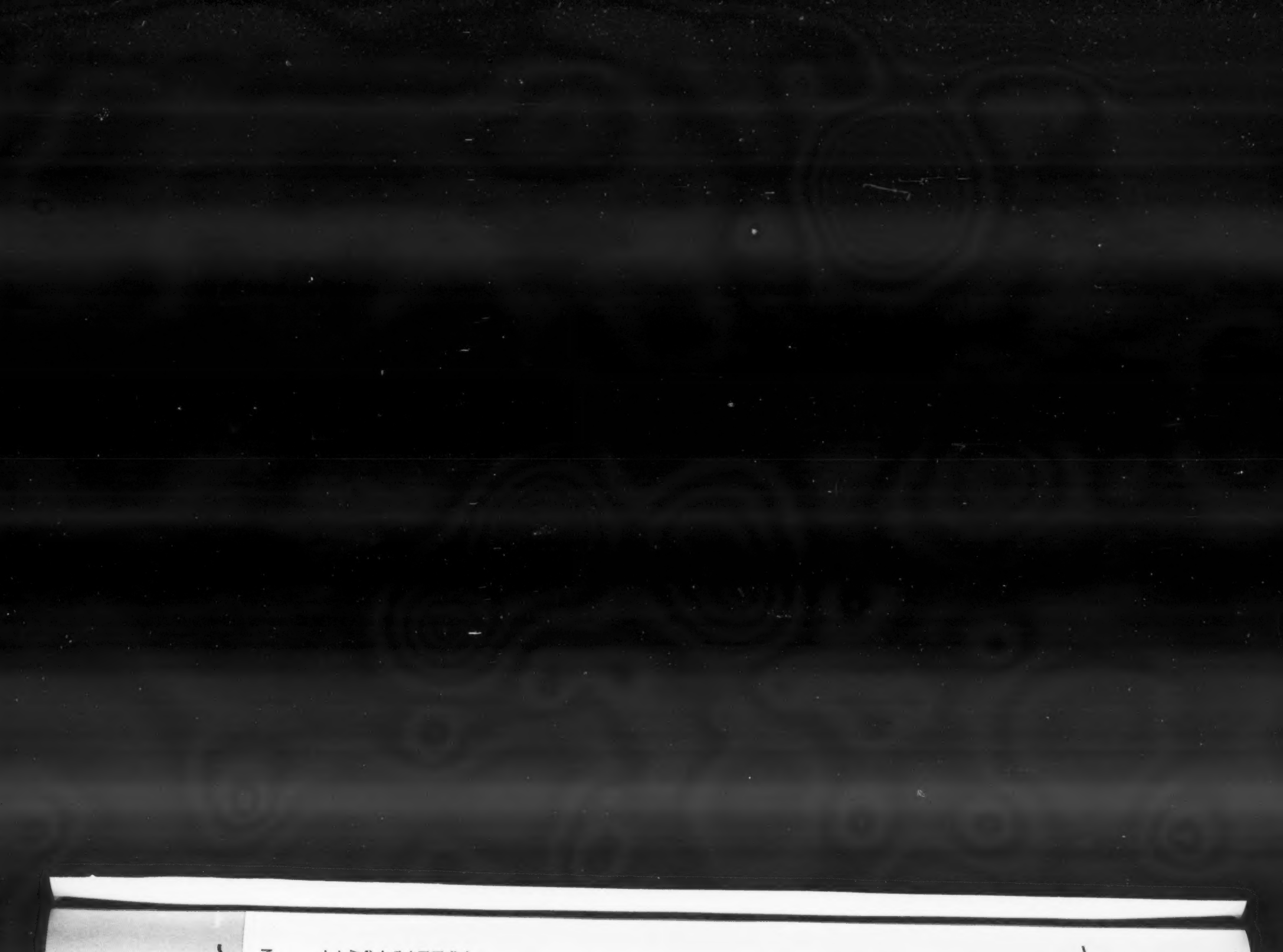
Are you concerned about adequate chemical disinfection of catheters? So much has been in the literature recently on the dangers of inadequate sterilization that we wouldn't be surprised if you were. To help you meet this problem, we have prepared an instruction card on O-syl® disinfectant specifically on this subject. The card is designed so that it may be posted for permanent instructions, or we will send you multiple copies for teaching purposes if you wish. Just let us know which you want. O-syl's broad microbicidal activity against a wide variety of enteriç organisms as well as Staphylococci, Pseudomonas, and TB bacilli recommends it for this use.

Focusing their attention on gram-negative bacilli, Dr. Hans H. Zinsser and his co-workers from the Department of Urology at Columbia University College of Physicians and Surgeons report alarmingly high mortality from septicemias due to urinary infections as follows: E. coli bacteremias, 38%; Aerobacter aerogenes, 60%; and Pseudomonas aeruginosa, 75%. While they were successful in reducing mortality from Aerobacter aerogenes septicemia in 1958 and 1959 60%, the incidence increased 300%, pointing up the great need for combatting the changing bacterial flora in the hospital with aseptic cleanliness. (The Journal of Urology, page 755, May, 1960)

Some of you will be reading this letter before the American Hospital Association meeting in San Francisco and some afterwards. Others may be seeing it before the American Public Health Association meeting, which is also in San Francisco this Fall. If you are at either of these meetings, we hope you will stop and visit us at our exhibit booth.

Charles F. Manz
General Sales Manager
Professional Division

LEHN & FINK PRODUCTS CORPORATION
4934 LEWIS AVENUE, TOLEDO 12, OHIO



Dear Sirs:

Proprietary and Nonproprietary Names

DEAR SIRS: I was pleased to read your editorial on proprietary and nonproprietary names for drugs in the June issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY, and I think that it would be of great interest to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations dealing with the selection of names. I would appreciate it, therefore, if you could send us six copies of the JOURNAL which I will distribute to them, or otherwise grant me permission to photocopy your editorial and send it to the members.

P. BLANC, *Chief Pharmaceutical Officer*
World Health Organization
Geneva, Switzerland

DEAR SIRS: Board member, Bob Gillespie, has advised me that the June issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY has excellent articles, on pages 380 and 331, discussing the proprietary and nonproprietary names for drugs in relationship to the professional responsibility of the pharmacist.

If possible, please send me tear sheets of these articles.

O. K. GRETTENBERGER, *Director*
Drugs and Drug Stores
Michigan Board of Pharmacy
Lansing, Michigan

From Argentina

DEAR SIRS: As president of the official pharmaceutical Association of Tucuman, that is the group of pharmacists employed by the Ministry of Health (public) and Social Assistance of the Province of Tucuman, Argentine Republic, I would like to tell you something about our organization. Our Association has been created with the prime motive to raise the cultural and scientific level of the pharmaceutical profession for those of us who work in the hospital service; we have regular meetings in which we discuss the latest and most advanced matters relating to pharmacy and allied fields.

. . . we would like to receive your publication, the AMERICAN JOURNAL OF HOSPITAL PHARMACY . . . These publications are of great interest to us because they will assist us in the furtherance of our profession and will be of interest to our members.

Our members, all of them pharmacists, are employed by this Province and are in the pharmacies of the following hospitals: Padilla, Santillan, del Nino Jesus, Maternidad (Capital); and also the following hospitals which are in the Province: Monteros, Concepcion y Famailla.

We would like to receive these publications on an exchange basis, that is we would be glad to send you all publications that we put out in the future from our pharmacy college of which I also am president.

We thank you in advance for your kindness . . .

PEDRO OSCAR DE CAMILLO
Las Heras No 187
San Miguel De Tucuman
Republica Argentina

Compliments

DEAR SIRS: This is to express my compliments on the layout and contents of the June 1960 issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY. I read this issue several times and each time felt that more had been gained by me.

Again permit me to repeat my compliments to you for the excellence of your JOURNAL.

MEYER USHKOW, *Vice President*
Endo Laboratories Inc.
84-40 101 St.
Richmond Hill 18, New York

Pharmacy in Portugal

DEAR SIRS: I was pleasantly surprised to read the article on Hospital Pharmacy in Portugal which was printed in the June issue of your publication.

This article would appear to be the companion of our historic sketch of Portuguese Medicine published in the May issue of Pfizer *Spectrum*.

Dr. Eric W. Martin, Executive Editor of *Spectrum*, joins me in sending you congratulations for recognizing the importance of foreign pharmacies and for informing United States readers about the standards of pharmacies in foreign lands.

E. I. JULIET, M.D., *Medical Editor*
Pfizer Spectrum
Pfizer Laboratories Div.
Chas. Pfizer and Co., Inc.
Brooklyn 6, N.Y.

VIRTUALLY NO DECREASE IN STAPHYLOCOCCAL SENSITIVITY

OVER AN 8-YEAR SPAN...TO

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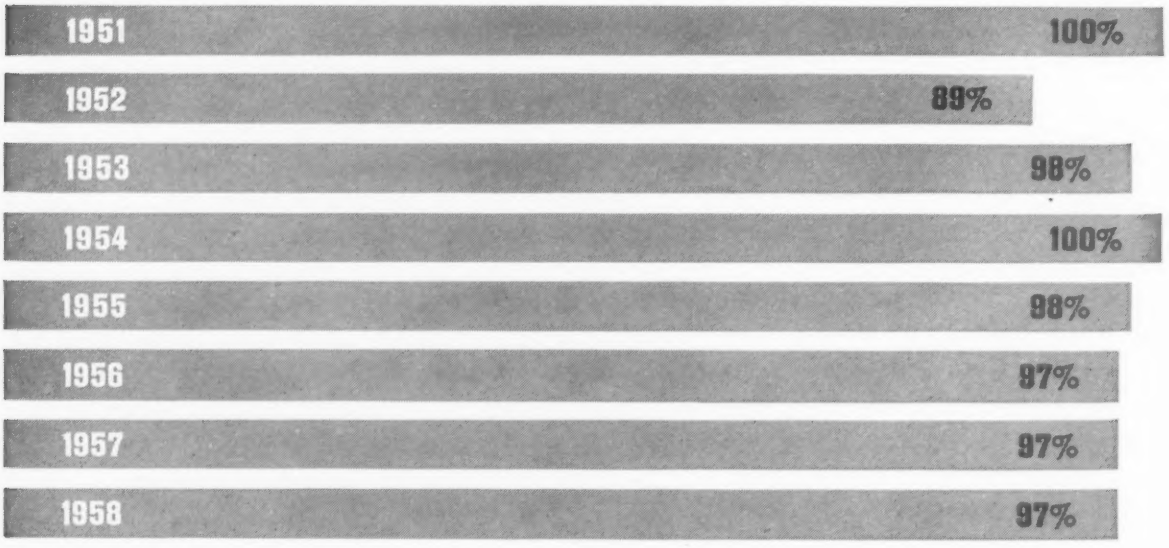
(chloramphenicol, Parke-Davis)

IN VITRO SENSITIVITY OF PYOGENIC STRAINS OF STAPHYLOCOCCI TO CHLOROMYCETIN OVER A PERIOD OF EIGHT YEARS*



Statistics were gathered over almost a decade on 329 children with staphylococcal pneumonia; 1,663 sensitivity tests were performed.

*Adapted from Rebhan, A. W., & Edwards, H. E.: *Canad. M. A. J.* 82:513, 1960.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

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by DON E. FRANCKE

The ASHP Takes A Stand On Outpatient Prescriptions

▶ ONE OF THE IMPORTANT DEVELOPMENTS OF THE 1960 annual convention of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS was its adoption of an official statement of policy regarding the filling of outpatient prescriptions. Heretofore, the only expressed policy of the SOCIETY was the statement in the Elaboration of the Minimum Standard for Pharmacies in Hospitals which was expressed in the form of resolutions in 1953 and 1954. The resolution, passed in 1953, is as follows:

Whereas the American Pharmaceutical Association went on record as opposing the filling of prescriptions for private ambulatory patients by pharmacies of tax-free institutions, and

Whereas the SOCIETY reiterates the policy as outlined in the Minimum Standard which reads as follows:

"Only those orders and prescriptions originating within the hospital should be filled by the hospital pharmacy. Prescriptions written by physicians who are not members of the hospital staff should not be filled by the hospital pharmacy," therefore

Be it resolved that the SOCIETY appoint a committee to study considerations involved in filling prescriptions for private ambulatory patients.

It is obvious that this resolution was only a partial answer to the need for a policy statement. In essence, it states that hospital pharmacies should not fill prescriptions for patients whose physicians are not members of the hospital staff. In effect, it opposes the opening of hospital pharmacies to the general public when neither the patient nor his physician has a direct connection with the hospital. Left unstated, however, was a more inclusive policy statement regarding outpatient prescription service.

There is, however, a suitable general statement on outpatient prescription service contained in the Elaboration of the section on *Organization* of the Minimum Standard for Pharmacies in Hospitals where it is stated that:

"Obviously the pharmacy department must be integrated with the general services supplied by the hospital of which it is a part. Where outpatient service is given, the hospital pharmacy should include outpatient prescription service."

During the past several years, numerous national, state and local pharmaceutical organizations have passed resolutions condemning the filling of prescriptions for non-indigent outpatients by hospital pharmacies. In fact, one board of pharmacy, Pennsylvania, has proposed a ruling which would make it illegal for hospital pharmacies to fill prescriptions for other than indigent patients and would even prohibit the filling of prescriptions for employees of the hospital. This proposed ruling is as follows:

A Hospital Pharmacy shall fill prescriptions only for the hospital inpatients and for persons admitted to its clinic as out-patients for treatment by a staff physician of that hospital on a subsidized basis. Such prescription shall not be compounded or dispensed to or for any other type of outside persons or patients or outpatients. (Employees and relatives of employees are included.)

By "clinic outpatients" is meant any person who is formally admitted to the clinical service of a hospital for diagnosis or treatment on an ambulatory and non-emergency basis in a formally organized unit of a medical or surgical specialty or sub-specialty.

By "outpatients treated . . . . . on a subsidized basis" is meant any outpatient who by reason of indigence, crippling disability, old age, or like economic or physical condition, is entitled to and receives the medical services of a hospital staff physician at a rate less than those charged in the ordinary case of a private outpatient who is admitted to the clinic for the convenience of his physician.

Boards of pharmacy which attempt such actions as this serve the interests of neither the public nor the profession as a whole. In fact, the proposal of such a ruling places into sharp focus the question of possible conflict of economic interest by a state agency created to serve the public health. The final disposition of this ruling should prove most interesting in clarifying the role of boards of pharmacy.

The SOCIETY's position on outpatient prescription service has now been clarified by passage of the following resolution:

Whereas ministering to the needs of the sick has always been a matter both for charitable endeavor and for economic gain, and

Whereas members of the public health professions have traditionally ministered to both prince and pauper, and

Whereas people of all economic strata utilize the facilities and services of the modern hospital, of which the pharmacy and its pharmacist are, and must remain, integral and inseparable parts, and

Whereas it is inevitable that, due to the complexities of modern medical care, all members of the health professions serving in hospitals will be called upon to play an increasingly important role in ministering to the health needs of the people, working through the organized hospital wherein each profession must fulfill its destiny, therefore

Be it resolved that the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, in annual convention assembled, asserts and believes that hospital pharmacists have unquestionable and unchallengeable moral, legal and ethical rights to serve patients, both indigent and non-indigent, by filling prescriptions written by members of the hospital's medical staff for outpatients.

This forthright resolution is a clear statement which should remove much of the confusion which has prevailed for years.

Equipment and Techniques for STERILE DISPENSING OF OPHTHALMIC SOLUTIONS

by PHILIP R. HUGILL, BORIS J. OSHEROFF *and* MILTON W. SKOLAUT

► RECENT ADVANCES IN THE FIELD OF STERILE preparation and dispensing of ophthalmic solutions have been tremendous. These advances have been not merely those of pharmaceutical elegance but rather of pharmaceutical necessity. One of the most outstanding articles pointing out the background for this necessity was that of Reigelman, Vaughan, and Okumoto.[1] "... corneal ulcers, they are such devastating infections that every possible measure must be taken to prevent them."

The necessity of dispensing ophthalmic solutions in a sterile condition has been conclusively proven. Sterility should be maintained during use of the solution.

The *British Pharmacopoeia* specifies sterile ophthalmic ointments;[2] and the *British Pharmaceutical Codex Formulary* requires ophthalmic solutions to be dispensed in previously sterilized containers and freshly prepared with aseptic precautions.[3]

The American Medical Association's Council on Drugs requires commercially manufactured ophthalmic solutions to be sterile in order to obtain Council approval.[4]

The U.S.P. XV[5] and N.F.X.[6] describe ophthalmic

PHILIP R. HUGILL is Staff Pharmacist and MILTON W. SKOLAUT is Chief, Pharmacy Department, Clinical Center, Bethesda, Maryland. BORIS J. OSHEROFF is Assistant to Chief, Research Branch, Division of Health Mobilization, Washington, D. C., Department of Health, Education, and Welfare, U. S. Public Health Service.

ALL PHOTOS COURTESY NATIONAL INSTITUTES OF HEALTH

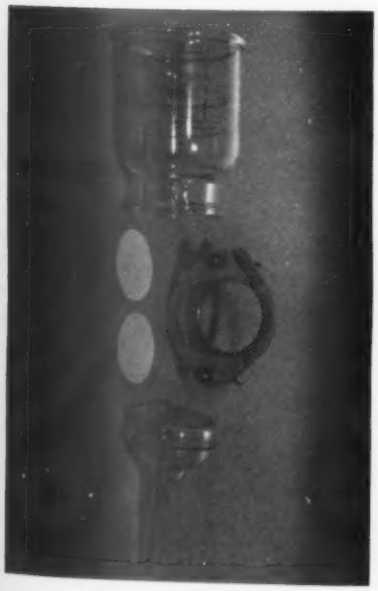


FIGURE 1. MILLIPORE FILTER with 47 mm. diameter membrane. (Millipore Filter Corporation, Bedford, Massachusetts)

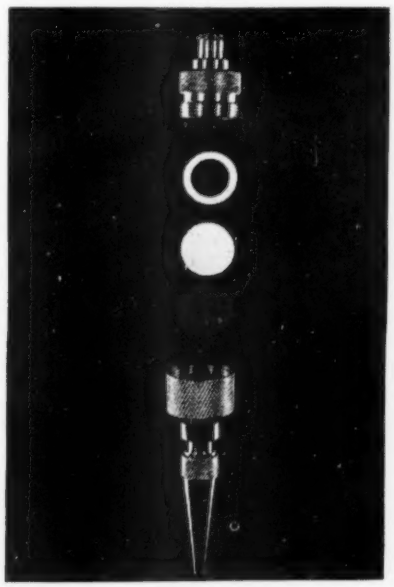


FIGURE 2. MILLIPORE MEMBRANE (13 mm.) in a Swinny Syringe Adapter

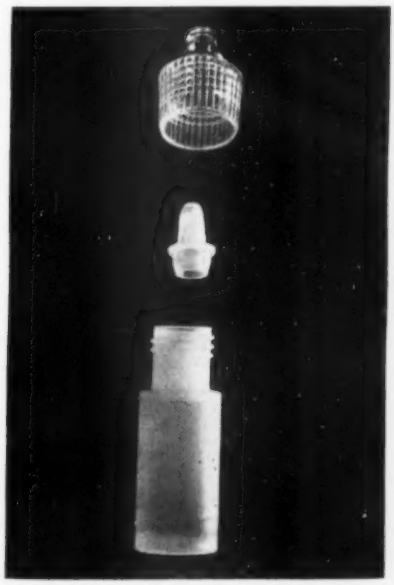


FIGURE 3. POLYETHYLENE DROPPING BOTTLES. (T. C. Wheaton Company, Millville, N.J.)

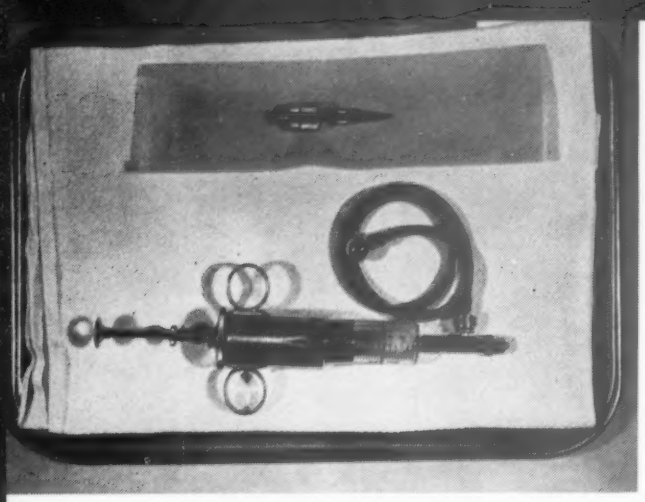


FIGURE 4. EQUIPMENT FOR EXTEMPORANEOUS STERILE FILTRATION

1. Prepared solution to be sterile filtered.
2. Clean luer-lok control syringe, 10 ml.
3. Swinny Millipore Filter attachment assembled with fistula tip and 0.45 micron filter membrane. This portion is packaged in a glassine envelope, previously sterilized by autoclaving.
4. Sterile polyethylene ophthalmic containers appropriately labeled.

FIGURE 5. EXTEMPORANEOUS STERILE FILTRATION EQUIPMENT with an optional two-way valve for continuous multiple filling.

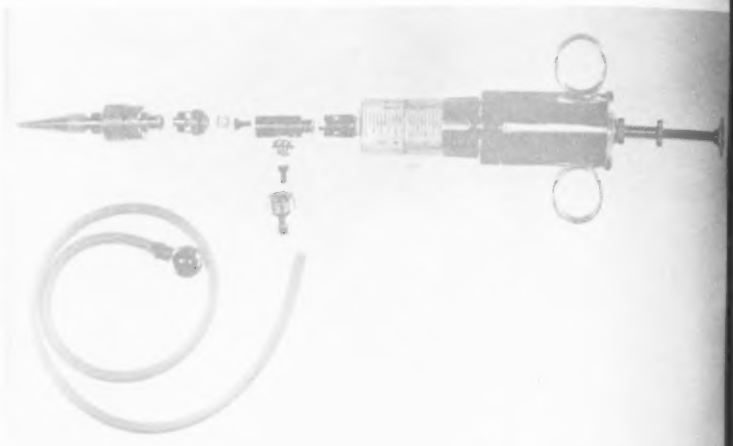


FIGURE 6. EXTEMPORANEOUS EQUIPMENT IN USE WITH SUGGESTED PROCEDURE.

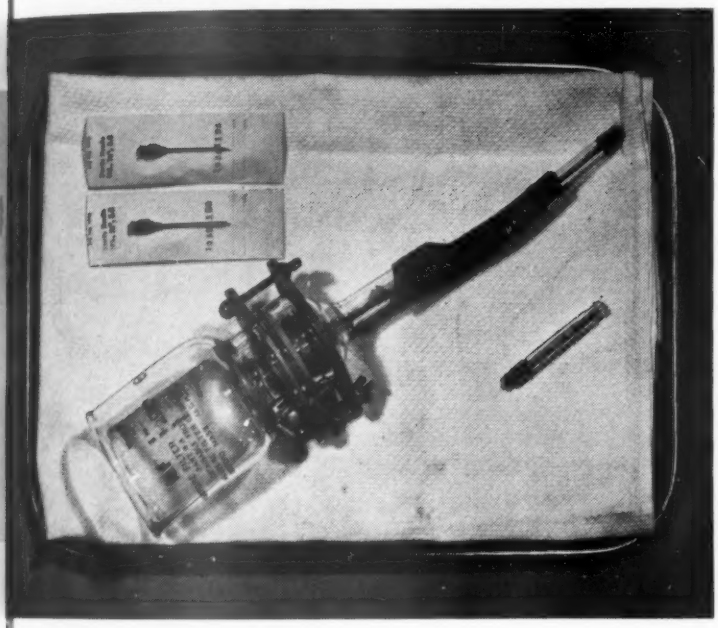
1. Clean area (a dust free area cleaned with an antiseptic solution just prior to use.)
2. Prepare control records and label bottles.
3. Prepare solution.
4. Open sterile package containing Swinny Millipore and attach to tip of syringe (plunger not in syringe)
5. Open sterile ophthalmic bottles just prior to individual filling.
6. Fill barrel of syringe by pouring solution, insert syringe plunger, and express solution through filter into containers.
7. If necessary to refill syringe, remove Swinny adapter with Millipore Filter from syringe before removing plunger.
8. Attach Swinny Millipore to barrel.
9. Refill syringe.
11. Close ophthalmic bottles with plug and protective cap.
12. Clean equipment immediately after use and resterilize.

For maximum utilization of equipment it is essential that the equipment be cleaned and sterilized for reuse as an integral part of the procedure.

FIGURE 7. STERILE FILTRATION TRAY AND SETUP.

1. Sterile Millipore funnel* of 250 ml. capacity assembled with filter pads (47 mm.).
2. Four inches of sterile amber pure gum surgical tubing 5/16" x 3/32" attached to funnel of millipore filtration apparatus.
3. Sterile Luer-lok observation tube inserted into free end of surgical tubing.
4. Second sterile Luer-lok observation tube containing non-absorbent cotton.
5. Two 16 gauge, 1½" sterile needles.
6. Sterile I.V. bottle with two hole solid rubber stopper and airway.
7. Vacuum pump with trap, or any source of suction at 10-14" Hg.

*Millipore funnel clamp shown has been modified.



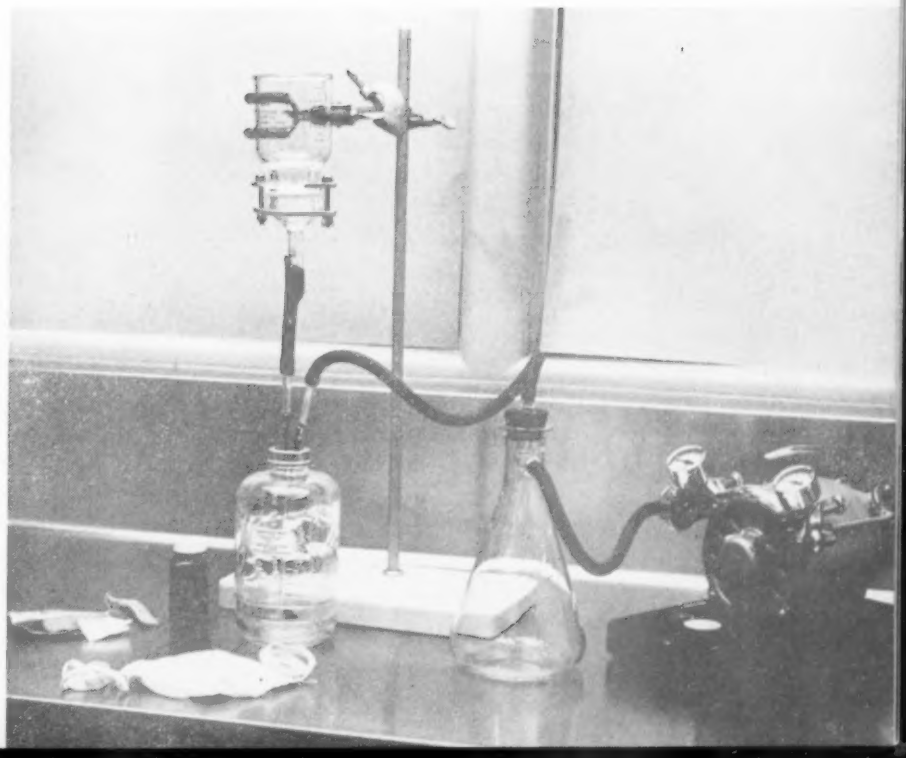
solutions as being sterile, preferably isotonic, with the addition of a suitable substance to prevent growth or destroy bacterial contaminants introduced during treatment with multiple use containers.

The organism which may be considered the major offender in ophthalmic preparations is *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), which can cause the most serious type of corneal ulcer. In 1943, Dr. Earl H. Brown made the following statement in the *Archives of Ophthalmology*: "For years, in going over the literature on corneal ulcer, I have noticed that all standard textbooks agree on one point, that corneal ulcer is a malignant disease and when due to *Bacillus pyocyaneus* usually leads to loss of the eye or at least to loss of sight."[7] Eight years later, eye medications contaminated with *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) were withdrawn from the market on two occasions.[8] Both preparations had been available to patients for some time. The implications of this need no clarification.

In the clinical experience of Frederick H. Theodore, M.D., as stated in the *American Journal of Ophthalmology,* May 1952[9] "almost every Pseudomonas infection encountered was due to contamination of eye solutions, or possibly ointments. In fact, it is amazing how few clinical infections actually do occur in view of the many times we have found abundant growth of the bacteria in such eye solutions." Another summary of the situation was written by John T. Murphy, *et al.*,

FIGURE 8. FILTRATION PROCEDURE

1. Label sealed, empty sterile I.V. flask of appropriate capacity, which is to serve as receiver.
2. Test vacuum pump.
3. Select ring stand that will hold sterile Millipore funnel.
4. Using sterile gauze, swab, rubber diaphragm of receiving flask with antiseptic.
5. Operator scrubs and wears face mask.
6. Open sterile tray. Remove funnel and clamp in position.
7. Open first needle envelope, and insert needle into "air vent" of receiving flask.
8. Attach observation tube on funnel to needle.
9. Open second needle envelope, insert needle into "solution hole."
10. Attach second observation tube (filled with non-absorbent cotton) to needle, and attach vacuum hose to this observation tube.
11. Pour 100 ml. of solution slowly down side of funnel.
12. Start vacuum pump and adjust vacuum to about 10 inches (Hg).
13. Refill funnel as necessary, never allowing filter membrane to become dry.
14. At completion of filtration, withdraw vacuum needle from receiver and then withdraw delivery needle.
15. Turn off vacuum pump.
16. Sterile solution may be stored in this flask until convenient to proceed with packaging operation.



in the *Archives of Ophthalmology,* January 1955,[10] "The irony of transmitting disease by measures intended for its prevention is abhorrent to all physicians. A growing awareness among ophthalmologists of the disease-producing role of contaminated eye medication is reflected in recent publications by Theodore,[8] King,[11] and Vaughan.[12] In view of the catastrophic results of drug-borne infections, ophthalmic medications must be prepared with aseptic precautions, sterilized after preparation, provided with an anti-microbial preservative, handled in such a way as to minimize the possibility of bacterial or viral contamination, and cultured at intervals to determine the effectiveness of these measures."

Background

The skills and equipment necessary for a pharmacist to prepare sterile ophthalmic solutions have always been available; unfortunately the equipment was cumbersome, the procedure expensive and time-consuming.

Developments in technology have made it possible for pharmacies to prepare sterile ophthalmic solutions, prepackaged and extemporaneous, at little expenditure of time and money. Not to adhere to high standards for ophthalmic solution preparation virtually borders on malpractice for any pharmacist, whether engaged in large or small volume preparations.

In the Pharmacy Department, Clinical Center, National Institutes of Health, several methods of preparing sterile ophthalmics were evaluated, including the methods used in the preparation of small volume injectables.[13] The procedure adopted employs the Millipore Filter (MF) for sterilization of the solutions and a previously sterilized polyethylene dropper bottle for packaging.

Methods

The basis of the sterilization procedure is the Millipore Filter.[14] This is a membrane consisting of cellulose esters with a selected maximum porosity of 0.45 microns. This pore size acts to retain physically organisms more than 0.45 microns in size, which includes all known pathogenic bacteria and mold life. The two sizes found most adaptable for use are:

47 mm. diameter membrane (See Figure 1)

13 mm. diameter in a specially honed Swinny Syringe Adapter (See Figure 2)

In all cases the membrane is supported by a porous rigid backing.

The ophthalmic solutions are dispensed in sterile polyethylene dropping bottles of a ¼ ounce capacity (Figure 3). They are procured sterile, packaged in a polyethylene bag, 144 per package. The sterility of the contents is protected by an outer rigid plastic threaded cap. Under the cap, when received, is an inverted polyethylene friction plug with a 1/32" aperture, backed by a polyethylene baffle to aid in forming uniform drops. In capping the filled bottle, the plug is reversed, seated in the neck of the bottle, and closed and protected by the threaded plastic cap.

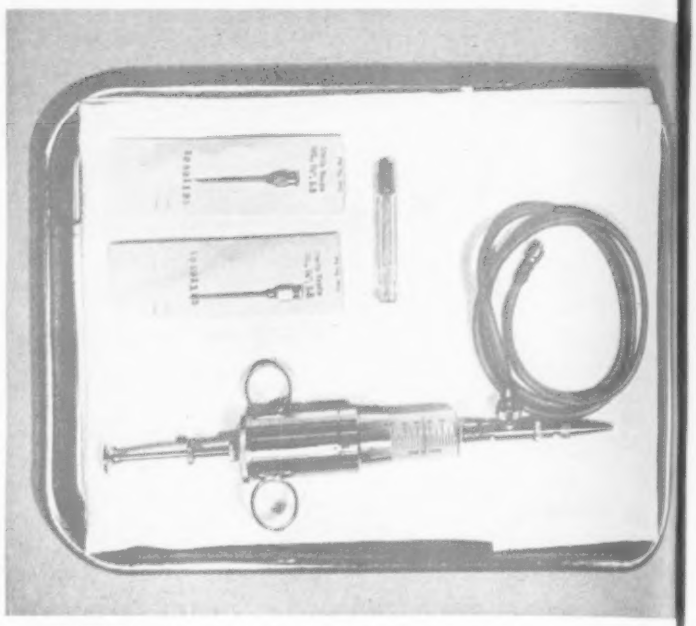


FIGURE 9. PACKAGING (TRANSFER EQUIPMENT TRAY.)

1. Luer-lok control syringe, continuous pipetting device.
2. Two-way valve with Luer-Lok adapter.
3. Luer-lok adapter on end of rubber tubing attached to inlet of valve.
4. Fistula tip attached to outlet of valve.
5. Luer-lok observation tube filled with non-absorbent cotton.
6. Two-16 gauge, 1½" needles, sterile.
7. Dust free hood and source of ultraviolet germicidal light.
8. Rack for filled bottles.

In using the package, the outer protective cap is removed, and the bottle is inverted over the site of application. Drops are expelled upon gentle pressure on the body of the bottle.

Following are several equipment sets with accompanying photographs showing simple, inexpensive and efficient materials for the preparation of extemporaneous and prepackaged sterile ophthalmic preparations.

Prepackaged Ophthalmic Solutions

The first consideration in the prepackaging of sterile ophthalmics is the routine compounding and sterilization of the product. It is not the purpose of this paper to delve into the techniques utilized for chemical and bacteriological stabilization of the solutions other than the following: In the preparation of the solutions all unnecessary exposure to light and heat are avoided, since many alkaloidal products are affected. Wherever possible, a suitable bacteriostatic agent is added to preserve sterility after opening.

The sterilization of the solution is accomplished by sterile filtration, if possible. Criteria for the determination of the feasibility for sterile filtration are: (1)

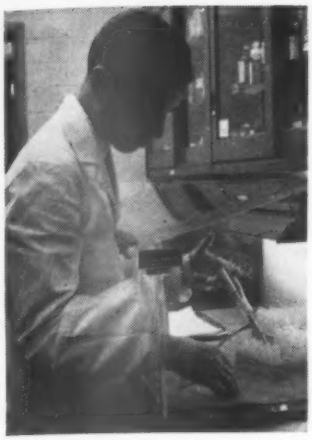
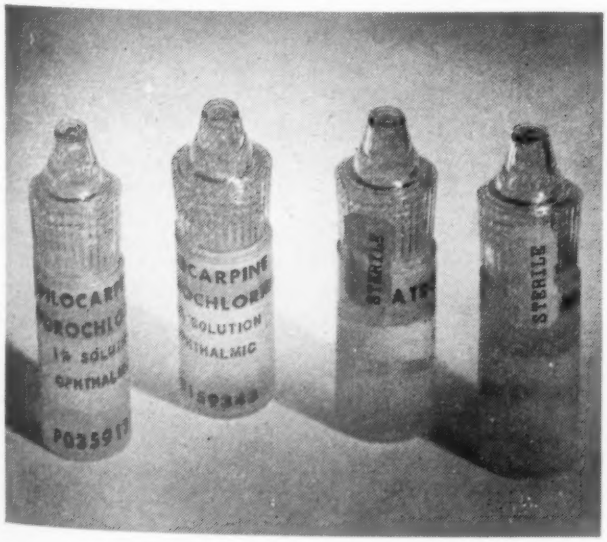


FIGURE 10. PACKAGING (TRANSFER) PROCEDURE.

1. Turn on ultraviolet light in hood for 30 minutes.
2. Turn off ultraviolet light.
3. Assemble racks for ophthalmic bottles in hood, suspend I.V. flask in metal cannister.
4. Insert sterile cloth sleeves.
5. Turn on ultraviolet light for additional ½ hour.
6. Enter hood through sleeves, wearing sterile surgical gloves.
7. Open tray and expose contents.
8. Open ophthalmic containers, placing containers in rack, and tops, caps, and plugs on equipment tray.
9. Open first needle package, insert needle into solution hole, and attach pipetting outfit to needle.
10. Open second needle package, attach needle to observation tube filled with non-absorbent cotton, and insert needle into airway of I.V. flask.
11. Turn off ultraviolet light.
12. Proceed with pipetting operation.
13. Close ophthalmic containers.
14. Clean equipment and re-sterilize.
15. Select packaged ophthalmics for sterility testing, and store balance in a quarantine area until sterility of product is established.

FIGURE 11. LABELING. When sterility is confirmed, the prepackaged units are labeled on the offset printer.[15]



viscosity and (2) particle size, in case of suspensions. Those preparations deemed not suitable for sterilization by filtration are sterilized by another effective method.

Storage and Dispensing

Packaged ophthalmics are stored in a refrigerator prior to dispensing, except for those which are not stable at lower temperatures.

Dispensing procedure indicates 30-day expiration dates on most preparations. In the case of outpatients who are supplied with multiple containers, directions are given as: "Discard 30 days after opening."

Conclusions

1. It is imperative that pharmacists, in the best interests of patient care, dispense only sterile ophthalmic preparations.

2. Sterility can be maintained under conditions on the nursing unit and in the patient's homes as well.

3. Inexpensive equipment is shown with appropriate procedures for hospital or retail pharmacy use.

4. The utilization of these procedures is not beyond the resources of any pharmacist.

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III. Stability of Medicaments

PHYSICAL DETERIORATION OF MEDICAMENTS

by M. GUILLOT

► TO TELL THE TRUTH, IT IS RATHER DIFFICULT to establish indisputably a clear difference between physical and chemical deterioration of medicaments. In fact, physical dimensions are introduced every time one undertakes measurements in chemistry; but we cannot say that it is the matter of a phenomenon which is exclusively physical, just because pressure, temperature, conductivity or other well defined physical dimensions are taken into consideration and give rise to measurements. It would be more accurate to say that there is a *chemical* phenomenon when a change of the molecular structure of the compound under consideration takes place, and a *physical* phenomenon only in the case of a modification of the state of the molecules without a change in the chemical structure.

At any rate, in the present report, we will consider (1) the effects of radiations of every nature on medicaments, (2) the deterioration which may arise in the course of physical treatments corresponding to everyday pharmaceutical processes, and (3) the phenomena related to changes in the hydration and equilibrium states of medicaments constituting heterogeneous systems.

Instead of reviewing all the publications which have appeared regarding particular cases where these phenomena have occurred in technical pharmaceutical problems—which would be long and tedious—I thought that it would be preferable to try only to establish what our knowledge allows us, at the present time, to outline as an overall picture of the theoretical interpretations which can be given of current everyday phenomena.

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Effects of Heat and Radiations

First, we will examine the general effects of heat and radiations of every nature. However, we must consider ultrasonic waves separately: they are the result of a mechanical longitudinal vibration of the medium on hand, which generally is an aqueous solution or a dispersed system including an aqueous phase. Nevertheless, some attention will be devoted to ultrasonics, immediately following ionizing radiations, because of a certain analogy between the practical effects of both types of radiations, although they differ extremely in nature.

Theoretically, *electromagnetic* radiations differ only by their *wavelength* and by the quantities associated with this wavelength, that is, *frequency* $\nu = \frac{c}{\lambda}$ (c being the velocity of propagation of light through vacuum and λ the wavelength) as well as the *quantum* related to the radiation under consideration, a quantum being the smallest quantity of energy which may be imparted to or drawn from matter, $W = h\nu$, where h is Planck's constant. It follows from these relations that the longer the wavelength, the smaller the value of the quantum. In other words, the radiation photon will impart less energy to each absorbing molecule, when absorbed by matter. The two major laws which govern this absorption of energy are as follow[1]:

1. *Grotthus' Law* (1818): *A radiation is active only if it has been absorbed.* It follows from this absolutely general rule that when a substance is perfectly transparent to radiation, no effect will take place. Particularly, this will always be the case of light towards colorless substances

2. *Einstein's Law* (1908): The alteration contemplated and corresponding to a chemical reaction, *requires a certain energy transfer which, at least, must have a certain threshold value.* Radiation being active by virtue of the absorption of a single quantum by a single molecule, it will be necessary for this quantum to provide at least the necessary energy to cause the chemical transformation considered. Therefore, there will be a minimum $W = h\nu$ to which will correspond

Professor Guillot addressing the FIP Congress of Pharmaceutical Sciences

a *minimum frequency* and consequently a *maximum wavelength*. Theoretically, at least, all radiations of a shorter wavelength should initiate the reaction; those of a longer wavelength would be ineffective. In reality there is evidence of a sort of resonance, with the result that when the wavelength drops progressively below the critical value, the probability of absorption of the radiation—and consequently of the chemical transformation—increases first, goes through a maximum and then decreases subsequently when the frequency deviates too much from the critical frequency. This corresponds to the existence of a more or less *strong absorption band*.

This general mode of action of radiation, which acts only as a source of energy, is practically the only one to consider when it is the matter of luminous radiations, and almost the only one when it comes to ultraviolet radiations, at least those of a long wavelength.

This direct absorption of a photon by a molecule constitutes the starting point of the photochemical phenomenon proper. The molecule assumes a new state of energy: it has stored energy. We say it is *activated*. It may subsequently lose this energy in a variety of different ways:

—either by radiation emission, which will be the simplest deactivation process. We may say in this case that there has been no radiation effect.

—or, on the contrary, by molecular collision, due to agitation, when it strikes another molecule. The stored quantity of energy will then become available and will facilitate the chemical reaction between the two molecules which have collided. An endothermic reaction may even be possible. In fact, it is the sum of the energies of molecular agitation and activation which will come into effect.

But, at this point, we must consider the other possible processes, and we will see that they are relatively large in number.

Action of Heat

First of all, the action of *heat* is closely related to the action of *radiations*. When a body or a complex system is heated it is supplied with infrared photons, that is, it is submitted to irradiation. All mineral or organic compounds do possess an infrared absorption spectrum. There is absolutely no substance without absorption, in this field. The more complex and dissymmetrical the molecules, the greater the number of their infrared bands. We may then say that *any* substance will absorb infrared. However, except in very rare cases, this absorption will not result in a photochemical action. There will simply be degradation of

the energy absorbed through transformation into heat, which means at the molecular level, that instead of an activation of the molecule—that is, a deformation with a change of its energetic state—there will be a modification of its *kinetic energy*: *molecular agitation* will be increased, and the expression of this energy of agitation is known to be (in the case of a gas):

$$\frac{1}{2} mv^2 = \frac{3}{2} \frac{RT}{N}$$

where,

- m mass of a molecule
- v its speed
- R gas constant
- T absolute temperature, t + 273°
- N Avogadro's number

v^2 is the average value of the square of the speed of the gas molecules. Therefore, v is called *average quadratic speed*. In fact, it is known that for a given constant temperature, the different molecules of a given volume of gas all have a different speed, the number of molecules for each speed being distributed in a bell shape curve, of the Gauss type. This means that if the majority of the molecules effectively have the speed indicated by the above formula, there are some with speeds much lower or much greater, their number being smaller as they deviate from the speed indicated by the formula. But there will always be *a few* with much greater speeds. A probability formula could be used, which would indicate, at each temperature, the proportion of molecules the speed of which exceeds a certain value. It is easy to understand, just by examining a Gauss curve that, as the values of T increase, the number of molecules exceeding a certain arbitrary value increases extremely rapidly because of the very shape of this type of curve. This is a very important point in practice, about which attention has been drawn by Goldschmidt, as early as 1909.[2] Indeed, this is the only way to account for the fact that the rate of reaction of a chemical system is exponentially a function of temperature. The course of the phenomenon of molecular agitation remains the same in the case of a liquid or a solid medium, with solely a complication due to forces of cohesion. But we may say, in a very general manner, that for any system the rate of reaction doubles every time T is increased by a quantity variable with the system, but which is always in the order of 5° to 10°C.[3] As one would be inclined to think in the first place, the mechanism of heat effect being only a cause of increased speed of molecular agitation, it would be the *average* molecular kinetic energy which would determine the influence of temperature on the rate of reaction; this rate would then vary with the square root of T, that is, the variation would be very small with temperature. Vant'Hoff has shown that this was not the case, that the variation was exponential in nature, and that the temperature coefficient varied from 1.5 to 4, according to circumstances. Only the explanation by Goldschmidt demonstrates that what is important, is the very rapid increase in speed of the *fastest molecules*, and not the average speed.

Application to Pharmaceuticals

This fact of the variability of the temperature coefficient has a great deal of importance in pharmaceutical technique. Each preparation for which we must study storage conditions, constitutes a very definite chemical system. The overall reactions, which may occur inside of it, give rise to successive transformations of the system, which may be expressed by a certain all-inclusive reaction rate, sensitive to temperature and of which we should know the order so as to establish the expiration date of a medicament. But in order to determine the complete equation of speed in function of time and temperature, so as to be able to infer by calculation the particularities of storage at 20°, from experimental data obtained in a shorter period of time at a higher temperature (45° for example) *a law* must exist. That is, the chemical reactions taking place at 20° must be *identical* to those taking place at 45°. Now this is not always necessarily the case. If several reactions coincide, *each* will have a *different* temperature coefficient and the overall picture may well be bewildering and, *a priori*, uncomputable. This has been shown by Ooteghem and Steiger (1957)[4] in their work on aqueous procaine hydrochloride. The process of hydrolysis of this anesthetic is not identical at 20° and above 80° and the temperature coefficients so change that a rapid study of the system at 100°, for example, does not permit calculation of the rate at 20°.

We must, therefore, put infrared radiations strictly aside since they generate temperature changes only and consequently a rise of the molecular agitation, having itself effect on reaction rates.

Ultraviolet Light

As we reach the visible, by progressively increasing the frequency, the photochemical phenomenon begins to play a part because the quantum of energy related to the radiation reaches a sufficiently large value to confer new reactive aptitudes to the activated molecules. But, as mentioned previously, only if the molecule is absorptive will it be photosensitive, that is, *colored* bodies only should then be considered. Colorless or white bodies (those diffusing light without absorbing it) will not be photosensitive.

This general rule is sometimes deficient, and the photosensitivity of ethyl ether, with formation of peroxides, has been discussed by Schou.[5] Obviously, in this case, one is dealing with a colorless liquid and, consequently, ultraviolet only can be considered at

first sight. One must be aware of the fact that daylight, even diffuse, contains an appreciable proportion of ultraviolet, and that even when colored containers have been used the results may be odd. Certain chain reactions are sensitive even to a small number of photons and it is possible that a proportion of 1 percent or less of the radiation existing in daylight, in the form of ultraviolet, will be sufficient to cause photochemical effects. It is therefore very important, where colored containers are to be used, that an accurate optical investigation be carried out before any conclusions are reached.[6]

Another increase of the frequency eventually leads to the ultraviolet region. In this region every molecule absorbs more or less, those containing functional groups displaying a band in the 2000 to 4000 angstrom zone and the others, at any rate, bands in the further region of 1500 Å. We may say that in this region the effect of radiation absorption will not be, in practice, an increase in temperature. The effect of heat, therefore, will be negligible and the photochemical action will always decrease because of the high value of the quantum.

Ionizing Effect

But a new type of effect of radiation appears here—the ionizing effect. A gas or liquid molecule struck by a high energy photon may, instead of absorbing it and becoming activated, simply undergo the process of "exterior electron removal." The molecule will then split into a *pair of ions;* one of these, negative, is simply an electron which has been liberated, the other, the remainder of the molecule, bears a positive charge due to the loss of an electron. In the case of water, this positive ion will be designated by the symbol H_2O^+. One must notice that this type of *ionization,* in the *physical* sense of the word, differs entirely from *chemical ionization* caused by the fact that the solvent is polar; in the case of water it leads to the formation of H^+ and OH^- ions. In this second case the molecule is split into two large ions of opposite sign, under the influence of the solvent; a process entirely different from the "removal process," and which does not necessitate the action of a radiation.

Formation of Free Radicals

In fact, a third process is also possible, equally due to high energy radiations known as ionizing radiations—*formation of free radicals.* Again with water as an example, the ionizing radiation may split the molecule into two free radicals, which we will designate as $H^\cdot$ and $OH^\cdot$ and which will differ from H^+ and OH^- in the sense that they will not bear an electrical charge and will be isolated fragments of molecules with an *unsaturated valence.* From a practical standpoint there is a great difference. Free radicals will have a considerable aptitude to reactivity. They will either tend to reassociate to form water with liberation of energy or to *couple*: 2 $H^\cdot$ to form a H_2 molecule and 2 $OH^\cdot$ a H_2O_2 molecule. An ultraviolet radiation of a short wavelength is already capable of producing, in water or aqueous solutions, a small proportion of such free radicals. The more the wavelength is decreased, first through X rays then γ rays, the more the formation of such free radicals will increase. The most remarkable, from a chemical standpoint, is that when present *together* in a solution and according to the nature of the solute acting as a substrate, they may act upon such a solute either to oxidize it if potentially subject to oxidation ($OH^\cdot$ then is active) or to *reduce* it if potentially apt to reduction ($H^\cdot$ then acts as a reducer). Instead of considering a medium as with oxidative or reducing properties (characterized by the value of the definite oxidation-reduction potential) we will be dealing with a medium which will be *simultaneously* extremely oxidative and extremely reductive, its behavior varying with the substrate. The complexity of the reactions caused by highly energetic radiations is then easily understood. In the case of water for example, there will be coincidence of H_2O^+, OH^-, H^+, $OH^\cdot$ $H^\cdot$, H_2O_2, O_2 and H_2. and the organic molecules present will react upon these ions just to split into free radicals or to ionize.

Summing up, we will group under the term *photochemical phenomena,* some extremely different mechanisms which may, according to circumstances, take place separately or simultaneously. From the standpoint of the reactions initiated we must first distinguish between 2 cases:[7]

1. The case where the photon absorbed by a molecule causes a chemical transformation with a quantic yield equal to 1, that is, a single photon causes the transformation of a single molecule. It is the most frequent and most simple case. The reaction truly is of a photochemical nature (hydrolysis of monochloroacetic acid in aqueous solution).

2. When the reaction is endothermic, energy requirements per molecule are greater; the greater the requirements the more it will be necessary for a molecule to be animated of a high minimum speed in order for the excess energy supplied by the photon to be sufficient to cause the reaction. Collision will therefore be effective only in a very small number of cases and the quantic yield will become very small: in certain cases it drops below 1/1000 (action of oxygen on quinine salts in aqueous solutions).

3. In other cases, on the contrary, the quantic yield assumes a considerable value; it exceeds 10 and may reach 10^4 or $10.^5$ The photon, then, seems to play the role of a detonator capable of causing an explosion. In fact something analogous is taking place—a *chain*

reaction. A well known example is that of the action of light or of ultraviolet on the chlorine and hydrogen mixture. It is admitted that in a first stage the reaction may be written (1): $Cl_2 + h\nu \rightarrow 2\ Cl^{\cdot}$. Therefore there is formation of two free chlorine radicals. In a second stage these free radicals react with hydrogen giving rise to $Cl^{\cdot} + H_2 \rightarrow ClH + H^{\cdot}$. A free hydrogen radical is then liberated which will itself react with chlorine: $H^{\cdot} + Cl_2 \rightarrow ClH + Cl^{\cdot}$. and so on. By this process the absorption of a *single* photon by a chlorine molecule is theoretically capable to cause the transformation of an infinite mass of the mixture $Cl_2 + H_2$.

Besides, in certain cases, this process may be limited to the first stage; this is what happens in a photographic emulsion where the photosensitive BrAg crystal (because of a certain irregularity of its crystalline system) is decomposed into two free radicals, $Br^{\cdot}$ and $Ag^{\cdot}$. This only causes formation, in any place of the crystal, of a small metallic scrap, visible but by means of an electronic microscope; the photographic processing will then allow the system to develop further.

Energy Transfer

There are certain complex systems which give rise to a very peculiar phenomenon: the interaction of reactions accompanied by *energy transfer.* For example this is the case of certain polyvitamin preparations. A review article has been dedicated to reactions of this type by Scheindlin in 1958.[8] He has studied[9] the combination folic acid-riboflavin and noted a very curious phenomenon. As we know, riboflavin is yellow colored and consequently absorbs visible light. But an aqueous solution of pure riboflavin is stable and so is an aqueous solution of folic acid (which was predictable, this compound being colorless). On the contrary, a mixture of the two solutes gives rise to a great photosensitivity, even to artificial light, and even when the mixture is stored in yellow containers filtering only 5 percent of the radiation of wavelength shorter than 450 millimicrons. From this we may infer that visible light only is transmitted through this type of glass and that it can be the only factor responsible. Since riboflavin is colored we may therefore expect it to be absorptive. But incredibly folic acid alone deteriorates, whereas riboflavin deteriorates very little or not at all. The mechanism has been studied in detail and happens to be as follows:

Folic Acid + Riboflavin (yellow) —light→ Mixture of oxidation products of folic acid and leuco-riboflavin (white)

In a second step riboflavin is regenerated according to the following reaction:

Leuco-riboflavin (white) —O_2→ Riboflavin (yellow)

The authors have shown that the action of a photon was necessary in the first reaction, where riboflavin undergoes a *reduction,* whereas folic acid on the contrary undergoes an oxidation. However air oxygen has no effect upon the primary oxidation; it has only a *secondary* effect as a regenerator of riboflavin. We may, then, conclude through this mechanism that:

1. Folic acid alone does not deteriorate.
2. Deterioration may take place in the presence of light, even in the absence of oxygen.
3. A small amount of riboflavin is sufficient to initiate the alteration of a large quantity of folic acid.

A later work[10] was to show eventually that the reaction could be stabilized by adding certain antioxidants, such as butylhydroxyanisole and ethylhydrocafeic acid, at a concentration of 0.02 to 0.05 percent.

Riboflavin-Ascorbic Acid Phenomenon

A similar phenomenon has been noted with the combination riboflavin-ascorbic acid. It had been known for some time that it was photosensitive, following Hopkins' observations in 1937[11] to the effect that a sharp decrease in the concentration of ascorbic acid in milk was caused by the action of diffuse light upon riboflavin naturally contained in milk. The rate of deterioration of the acid was a function of the concentration of riboflavin.

Work by Hand and co-workers[12] in 1938 has shown that the simultaneous presence of air, light and riboflavin were necessary to such a decrease and that yellow glass was not effectively protective.

I have had the occasion, personally, to note a similar phenomenon[13] under still more curious conditions. From an aqueous solution of a mixture of the B complex group, containing moreover some vitamin C, we had prepared a "lyophilisate," which as usual appeared in a vacuum sealed ampul, in the form of a dry, porous residue, yellow by riboflavin. Exposure of this perfectly dried preparation to the sunlight caused an almost instantaneous superficial discoloration. However, after becoming white, the mixture would recover spontaneously its initial yellow color, if kept in the darkness for a few hours. Exposure anew to the sunlight caused discoloration and so on. A reaction similar to that previously mentioned was taking place: oxidation-reduction of the combination ascorbic acid-riboflavin, with probably the other B vitamins present taking part, particularly B^1, and, in a second stage regeneration of riboflavin.

Note that in this case there was no air and that the necessary oxygen was to be furnished by the *system.* A complete investigation of the reactions, undoubtedly manifold, has not been carried out but the catalytic effect of riboflavin in the photochemical reaction is obvious.

Photo Reactions of Ascorbic Acid

A remarkable example of a coupled oxidation-reduction reaction is that which has given rise to concise methods of analysis for the determination of ascorbic acid in the presence of a coloring agent.[14] In the method by Mentzer[15] the ascorbic acid solution to be determined is added to methylene blue and the solution is irradiated by a high powered glowing lamp. Methylene blue discolors to become a leuco-derivative, that is, it is reduced and simultaneously ascorbic acid undergoes oxidation. The reaction is stoichiometric and allows a determination by simple colorimetric evaluation of the methylene blue remaining intact; but it takes place only in the presence of light and air oxygen has no effect. In the method by Charonnat[16,17] the situation is quite similar with the combination thionine-ascorbic acid, the only difference being that an ordinary incandescent lamp is sufficient to furnish the necessary luminous energy, probably because the active photons have a much longer wavelength, although to our knowledge an optical investigation of the reaction has not been undertanke. Actually, this is not a matter of photochemical alterations but examples which help to better understand how light may act, in practice, upon systems of this type.

Cold Sterilization

As we can see, if the complexity due to photochemical reactions may be very great in the case of systems, as those above, where there is a large number of constituents, it may also lead to a bewildering multiplicity of reactions when all the mechanisms coincide even when the starting point is a single substance in solution. This is the case, for example, when ascorbic acid is irradiated with ultraviolet, as it has been shown by Douzou.[18] It is certain that these photochemical processes play an important role in living matter. In pharmaceutical technique they occur every time ultraviolet rays are used, and to a greater extent with X or γ rays, that is, every time we resort to what is now called "cold" sterilization, in order to destroy bacteria present in a preparation without a rise in temperature. We therefore agree that if these methods are effective against bacteria, molds and growths, they are also unfortunately apt to produce multiple chemical reactions of an alterative nature and it is also the same when γ rays are replaced by electronic radiations. Several technical investigations have been undertaken in recent years in order to introduce these new sterilization methods in the pharmaceutical industry. Reference is made to accounts I have had the occasion to present regarding this subject which we cannot discuss here.[19] I will simply mention that it is impossible to avoid a brown coloration along with a tendency to polymerization of medicaments to be sterilized as shown in a study by Barker, Grant, Stacey and Ward (1959).[20] Then, it is only in the case where a pharmaceutical preparation is already strongly colored, that the inconvenience of a brown color, due to the action of radiation, is of little importance and that electron sterilization may be utilized, so long naturally as stability of the active principles is verified along with the maintenance of their aptitude for long storage periods, as was done with polyvitamin preparations by Colovos and Churchill.[21] But in many cases the active principles lose potency[22] and a color change takes place simultaneously, as I have had the occasion to notice in the course of an unpublished work on sterilization assays of dry streptomycin sulfate by X rays and as have recently mentioned Bonet-Maury and Lormand about γ sterilization.[23]

Ultrasonics

It is now time to say a few words about ultrasonics, although their mechanism is entirely different, since in this case it is the matter of elastic longitudinal vibrations of the same nature as sonor waves, but without any relationship to electromagnetic radiations. However, the effects upon an aqueous solution are extremely similar to those of an ionizing radiation[24] since there is still formation of free radicals, formation which is more or less emphasized according to the presence or absence of air or oxygen. It had been thought to use ultrasonics as a mode of sterilization. This had to be given up because of the alterations which resulted from the formation of free radicals, and probably even more because of the influence exerted by the least variation in experimental conditions: gas in solution, presence of foreign ions or molecules, temperature, etc. It is extremely difficult to achieve reproducible experiments and consequently to introduce the use of ultrasonics in pharmaceutical technical processes. This is unfortunate, because, besides their important sterilizing power, they do have a remarkable dispersing power which should make them the process of choice in the preparation of suspensions and emulsions.

Electromagnetic radiation photons as well as rapid electrons and ultrasonics may therefore initiate reactions of the photochemical type and, very often, the intermediary compounds will be *peroxides*. Therefore a closer relationship takes place between the study of photochemical reactions and their analogues, the study of free radicals and the study of reactions of transitory formation of peroxides. This develops into a very special chemistry which in many cases is of interest to the pharmacologist.[25]

Synthesis of Macromolecules

We must now return to the problem of polymerization. We have seen previously, that one of the accessory effects of high energy radiations was to favor (catalyse) the formation of certain polymers. This property is

now being used extensively in industry for the synthesis of macromolecules. We may say, in a very general manner, when a small molecule is devoided of the property of binding to "fellow molecules" by lack of a convenient functional group, that the action of a radiation may be to create the necessary point of attachment on the molecule, thus favoring fixation to a neighboring mole. Very soon, at the end of the reaction, each mole becomes a link of the long chain constituting the macromolecule. The most general type of *polymer* will be *linear*;[26] in certain other cases the attaching points created on the molecule by radiations will be distributed in points indirectly opposite and the association will therefore take place in many directions in space, giving rise to a nonlinear polymer of the spheroidal type. High energy radiations have thus become current polymerization agents and one must not be astonished if they initiate analogous processes in a very large number of cases. When the same radiations exert their action on a linear polymer, for example, they may cause the rise—at indefinite locations along its chain or through peroxide groups—of some new points of attachment, for example, by replacing H by OH. In a subsequent reaction these sensitized locations on the molecule may become the point of origin of a *side chain*.

Such possibilities are of interest to us only as an accessory process. Even in the case of light accompanied by solar radiations, it is known that the photochemical effects of radiation will appear simultaneously in the form of oxidation and polymerization. With liquid terpene compounds, this double process will lead to the formation of "resins," solid amorphous "solutions" of terpenic acids, more or less complex and associated in the form of polymers. Should we proceed from the visible to the infrared region these phenomena will occur only as a first approximation. But in the case of certain fragile molecules they may still take place to a certain extent. This will correspond to the fact that the distillation of a complex organic liquid such as an essential oil—although it permits elimination of water and of various nonvolatile impurities—always presents the major inconvenience of causing the formation of a small quantity of oxidized polymers. Such polymers increase in quantity as the distillation proceeds and the final result of the operation is a resinous residue. The relationship between this inconvenience and the work by Barker and co-workers,[20] mentioned previously, is quite suggestive. Partial polymerization caused by the action of high energy radiations on various molecules and particularly on glucides, may also originate from radiations of a shorter wavelength, such as ultraviolet, and in certain cases even from light. But a single temperature rise, especially in the presence of oxygen, may also have the same effect. Polymerization, then appears as a very general mode of alteration, sometimes of a photochemical origin, sometimes of a thermal origin.

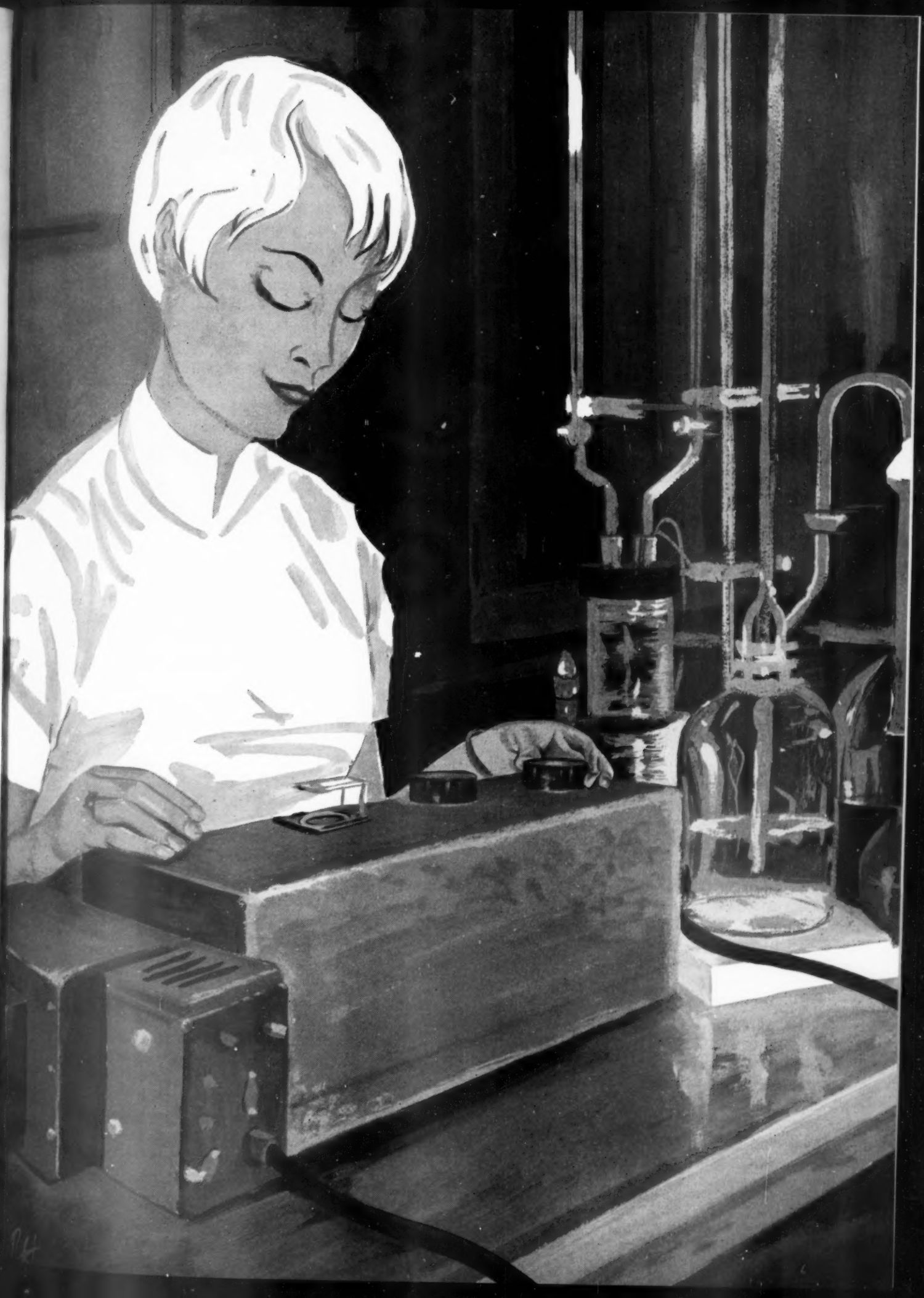
Oxygen and Light Affect Storage of Oils

There is a point which deserves to be emphasized. When visible or ultraviolet radiations initiate an oxidation-polymerization process, generally there is simultaneous action of surrounding oxygen and of radiation. If the system is protected against one or the other of these two factors the process is stopped.[27,28] I have had the occasion to study samples of a natural oil for six or seven years. Some were exposed to diffuse light, others stored in complete darkness. The experiment clearly indicated[29] that when the container was almost filled and kept away from light, no oxidation-polymerization took place even over several years. When the container was half filled and also kept away from light, one could notice some deterioration, whereas the same sample exposed to light, gave rise to considerable alteration; but, the well filled containers, although exposed to light, had alterated very little because of the very little amount of oxygen above the surface. It then seems that a well-filled container, even when exposed to diffuse light gives rise to insignificant alteration. This would then justify the practice in perfumery of adding glass beads every time some oil is removed from a container. These would compensate and cause the liquid to rise close to the top of the container.

If we wish to summarize in a few words what has just been discussed previously we may say that: "medicaments must be stored away from air, light and in a cool place."[30]

Humidity and the Storage of Drugs

To the above formula, we generally add "and in a dry place." And this leads us to discuss the physical constant related to moisture, that is, the hygrometric state. This is a practical matter of great importance. When the influence of water vapor upon a chemical system is considered, it is not generally the quantity of water vapor present in the atmosphere above the system that is important, but the hygrometric state of the air, that is, the ratio of the *partial pressure* of the water vapor in the air to the maximum pressure of this vapor at a given temperature (in other words, *vapor tension* at a given temperature). One may define the hygrometric state as the ratio of the mass of water contained in a unit of air volume to the maximum mass of water this air *could* contain, if it were saturated, at the same temperature. The hygrometric state is obviously expressed by a number comprised between 0 and 1 if the definition selected is as above and by a number between 0 and 100 if the preceding ratio is multiplied by the factor 100; instead of referring to "hygrometric degree" we then sometimes refer to "percent humidity."



Efflorescence

The most important phenomenon related to humidity, so far as the storage of drugs is concerned, is that of efflorescence and deliquescence of salts and of preparations containing salts. This is an entire chapter of galenical pharmacy which deserves clarification by a few remarks. A salt is said to be efflorescent when it gives rise, at the crystalline state, in air, to a partial or total loss of its water of crystallization, loss which causes a reorganization of the crystalline network since there is passage from a salt with n H_2O to a salt n′H_2O (where $n' < n$) or to an anhydrous salt. But all of the classical works insist on the fact that there are no salts which are *naturally* efflorescent (or nonefflorescent). Departure of this water of hydration in the form of vapor in the gaseous phase gives rise to a dissociation reaction, subject to the laws of thermodynamics. In the simplest case, where one is lead to a well defined inferior hydration state, there are two solid phases and obviously only one gaseous phase with a number of independent constituents equal to two and the phase rule indicates that the system is univariable. It follows that, for each temperature, there will exist an equilibrium pressure. It will not be the total pressure borne by the salt, but the *partial pressure* of water vapor in the air, so that even if all experiments are conducted at atmospheric pressure, this equilibrium pressure will vary in each case with temperature. If a salt is placed in an atmosphere with x percent humidity, at temperature t, and if the dissociation pressure of this salt is greater than the partial pressure corresponding to this x percent humidity, the salt will effloresce. If, on the contrary, its dissociation pressure is smaller it will not effloresce. Thus, this same salt when stored in "humid" atmosphere may or may not effloresce depending upon temperature and the exact value of the hygrometric state. This is exactly what experience shows, and consequently a salt in a tightly closed container will *never* effloresce notably; if at the beginning of the experiment the hygrometric state of the air in the container is insufficient there will indeed be efflorescence, but a rapid increase of water vapor in the atmosphere will take place and equilibrium will soon be reached; then the rest of the salt will necessarily remain intact. On the contrary, if the cap "leaks" and if water vapor is allowed to escape—even at a very slow rate—efflorescence will continue more or less slowly but in a continuous manner. Work by Diesnis[31] dating back to 1934 has stated precisely the conditions under which the principal salts used in pharmacy lose their property of efflorescence at ordinary temperature.

Deliquescence

The problem of deliquescence, closely related to efflorescence, is just the inverse. What must be taken into account here is the vapor tension (or maximum pressure) of the *saturated* solution of the salt, at the temperature under consideration.[32] If the partial pressure of water vapor in the environmental atmosphere exceeds this maximum pressure there will be a tendency to deliquescence and conversely. The paper of Diesnis has stated what was at 20°, the limit percent humidity of the air, compatible with the maintenance of a salt at a dry state, without deliquescence, this limit value being different for each salt.

If one establishes a relation between these two ideas, we come to this very general law, that any salt crystallizing with a certain number of molecules of water exists at a stable state at temperature t, between two values of the percent humidity. Above the higher limit, the air is too humid and the salt becomes deliquescent. Below the lower limit the atmosphere is too dry and the salt effloresces. For deliquescence as well as for efflorescence, storage in well-sealed containers is sufficient to prevent either of these alterations. A very important point in pharmaceutical practice is that the knowledge of these two limits, establishing the range of conservation of a salt, stands only if the salt is pure. But, for example, if we consider a mixture of two different chemical substances, such as ascorbic acid and sodium ascorbate, the limit values of the hygrometric state assuring the stability of the constituents individually, do not stand for the mixture, which is much *more sensitive* than each of the constituents. It follows that tablets of ascorbic acid and sodium ascorbate are much more hygroscopic than is either of the components.

Free-Flowing Salts

Everybody knows or at least has seen the trade names of table salt which has the property of flowing freely through the holes of the salt shaker, even under a slightly humid atmosphere, whereas ordinary fine salt agglomerates under the same conditions and refuses to flow. There is a very curious experimental fact which has been studied by Frey[33] in 1955 and which has given rise to special administrative provisions for sea salt. The addition of a small quantity (1 or 2 percent for example) of a foreign powdery substance, insoluble in water—a substance which will powder the crystals—allows crystals of the salt to slide one over the other and prevent agglomeration, even if it picks up some water molecules from the air. In the case of sodium chloride the substances used are tricalcium phosphate and magnesium carbonate. Experience shows that under the same conditions of humidity, the quantity of water absorbed by ordinary or specially treated salt still remains the same, but the former agglomerates while the latter remains "fluid," so long as the rate of humidity remains low. This artifact, therefore, does not eliminate deliques-

cence and does not modify equilibrium conditions, but it simply allows an accessory physical property—fluidity of the crystals—to subsist in spite of humidity. Besides, salt treated in this manner liquefies just as ordinary salt does. The method is, then, efficient only initially and in appearence, but it gives rise to a large number of industrial applications and it may be of interest to pharmaceutical technique in every case where it is desired to maintain the property of crystals "to flow" regularly, as is the case in tablet manufacturing.

Azeotropy

Fixation of atmospheric humidity by pharmaceutical preparations of a more complex nature is only a generalization of the preceding phenomena. It is known that many organotherapeutic preparations particularly, rich in polypeptides, are extremely difficult to preserve in a dry state under humid conditions. The same goes for peptones and certain enzymatic preparations such as pancreatin. Here also the procedure or artifact to be used is similar to that for salt. Preservation in rigorously sealed and well filled containers remains the most reliable precedure. But, in certain cases this is insufficient, and one must resort to preservation under vacuum in sealed tubes. Yet, vacuum desiccation causes problems. If the limit partial pressure of water vapor insuring stability of the dry product is very low, it is still possible that the action of desiccants such as calcium chloride and even phosphoric anhydride will be insufficient and that it may become necessary to eliminate the traces of water contained in such a product by some other procedure, say in the form of an azeotrope. Xylene, for example, is often used for this purpose. An unpublished observation kindly communicated by my predecessor, Professor Picon, concerned a bismuth salt, soluble in certain organic solvents, but only if previously totally dehydrated, since it became *insoluble* in such solvents if it contained a trace of water—a trace which it was impossible to remove by vacuum even in the presence of phosphoric anhydride for several weeks. This example shows that humidity sometimes creates enigmas.

Belladonna Extract

A classical example of deliquescence is that of certain extracts, and particularly that of belladonna extract. Abundance of deliquescent potassium confers upon it the property of picking up moisture from the air and becoming liquid very rapidly if it is not well protected.

Calcium Gluconate Solutions

We will now examine an entirely different problem, that is, supersaturation of solutions. The most current example is that of calcium gluconate. This salt is used in the form of concentrated aqueous solutions at 5 or 10 percent and assumes the form of an injectable. Its solubility is great at 100°, so that at this temperature it is easy to obtain an aqueous solution which is not supersaturated. It may then be filtered, filled into ampuls and easily sterilized. But afterwards, if the solution is cooled to 20° it is supersaturated. Experience shows that in a lot of ampuls so prepared, some, randomly, will crystallize, attaining generally all of the volume occupied by the liquid after a short period of time. Certain authors have been of the opinion that such ampuls could still be used provided they would be heated so as to cause solution. But it usually happens that crystallization will take place again upon cooling so that, in fact, one is forced to reject them. A cure has been found for this inconvenience: addition to the gluconate of a certain proportion of other calcium salts which increase solubility and stabilize the preparation. Thus U.S.P. XV authorizes the addition of calcium saccharate or of other inoffensive salts of the same metal. The *British Pharmacopoeia* of 1958 allows the same addition, so long as the concentration will not exceed 5 percent in terms of the weight of gluconate. The *International Pharmacopoeia* agrees with these views and authorizes 2.5 to 5 percent of the total calcium content in the form of saccharate. It also indicates a *modus operandi,* whereby the saccharate is dissolved in 4/5 of the hot water and then followed by the addition of the gluconate. Agitation is carried out until solution is complete, after which it may be allowed to cool without risk of crystallization. The volume is completed with distilled water. Filtration is made with the aid of fritted glass. The solution is placed into ampuls and sterilized. The *French Codex* gives no indications relative to stabilizers and the *Russian Pharmacopoeia* prescribes the preparation of a 10 percent solution to be boiled for three hours before it is filtered, filled into ampuls and sterilized. What has surprised certain pharmacologists is that when the gluconate solution is prepared according to a procedure similar to that of the *Russian Pharmacopoeia,* without the addition of a foreign salt and at a high concentration (10 percent) it is still possible to obtain ampuls which will keep for long periods. But, on the other hand, it seems difficult to understand why *certain* ampuls will crystallize following a very long period of stability, when the storage temperature has remained constant and when no exterior agents (agitation, shocks,) have had any effect. In order to furnish some explanation one must resort to the classical experiments by Tammann[35] (1903). In his opinion, *molecular agitation* will allow the casual assembly of the molecules of the solute, in relative positions, so that they somewhat duplicate those of the crystalline system of the solid substance. Thus a microcrystal will form haphazardly and immediately

will serve as a starting point to the formation of a crystal, since the solution is supersaturated. However, the *probability* of appearance of such a microcrystal will depend upon temperature. If it exceeds the temperature corresponding to the equilibrium concentration, that is, to a solubility equal to the concentration of the solute, there will be no tendency to growth and the phenomenon will not take place. When the temperature drops below this temperature of saturation, the probability of appearance of such microcrystals and of growth *will increase* and reach a maximum for a temperature about 50° below the equilibrium temperature. Should it still be decreased the phenomenon would progressively be slowed down so that the overall probability would *decrease*. Actually, the phenomenon is much less understood in the case of a solution than in the case of a pure substance in a state of superfusion. At any rate, this general explanation still holds, and, in our particular case, one may estimate that the usual 10 percent concentration corresponds approximately to an equilibrium temperature of about 85°. The optimum spontaneous appearance of the crystals would then be about 35° and this would explain why storage at 20° is less favorable to the appearance of microcrystals, and that at 10° it is still less, contrary to what would have been expected. In this case therefore, a severe drop in temperature does not necessarily cause crystallization.

Pulverization

Now, we still have to review briefly a certain number of causes of physical alterations, corresponding to pharmaceutical operations. We will talk first about pulverization. Very often pulverization of a given crystalline substance "in the cold" will cause the presence of an impurity to appear. We are naturally inclined to believe it is an alteration of the substance, caused by the mechanical effect of pulverization and eventually by a local temperature rise due to shocks.

I have had carried out in my laboratory, a long range project on that subject[36] (1934). The study of chemical systems of crystalline mineral compounds susceptible to interact, had already shown by X ray diffraction, that, in general, ionic reactions did not take place "in the dry" by simple pulverization, and that only in certain cases were they possible.[37] But the experiments by Chalchat have shown that prolonged trituration, "in the cold", of mercury bichloride never produced mercurous chloride, nor conversely did that of calomel produce mercuric chloride. Similarly kermes was not altered by prolonged pulverization and the majority of organic substances did not give rise to any alteration even when apparently such an alteration was obvious. Thus crystalline acetylsalicylic acid (aspirin) frequently evolves a clear odor of acetic acid. Therefore one expects to be in the presence of a slight hydrolysis due to traces of water in the crystals, which of course would liberate acetic acid and salicylic acid. But trituration of these derivatives, before and following pulverization, has shown that the potency remains the same and that if there is evolution in the air of acetic acid in the course of pulverization, it is simply because this acetic acid pre-exists in a free state in the crystals—pulverization having only the effect of facilitating its vaporization in the air. It has been established, also, that cocaine hydrochloride was not altered and that when pulverization of this salt caused evolution of benzyl benzoate—of a characteristic odor—it was because the crystals contained it in advance in the form of an impurity—benzoate in a free state. Besides, it has been possible to establish that desiccation of cocaine hydrochloride caused hydrolysis and was responsible for the presence of benzyl benzoate. Even more fragile substances, such as amygdaloside, solicoside or β-methylglucoside no more than vanillin do not give rise to alterations by pulverization "in the cold". Chalchat has even noticed that no tautomerisation of α-glucose or β-glucose resulted from pulverization "in the dry" and that optically active substances, such as hyoscyamine levorotatory, tartaric acid or emetic did not undergo racemization. It may be concluded from these overall observations that, in general, pulverization "in the dry" is of no danger to pharmaceutical products.

Racemization by Heat

If pulverization, in general, is incapable, as we have just seen, of causing racemization, it is not so with heat. A very large number of papers have been devoted to the alterations of optically active substances either at their dry state, or in complex galenicals. Application of heat to substances of such a nature, especially in the presence of moisture, and most of all when the medium is not rigorously neutral, may cause a more or less complete racemization. This is specially the case of hyoscyamine preparations.[38] They have given rise to several papers and we cannot cite them all here. [39,40]

Epinephrine

Racemization in solution is a phenomenon more well defined and which is obviously under the influence of certain physical factors. We will put aside the influence of *p*H which is more of a chemical nature. In an alkaline medium we may say that all optically active substances undergo racemization rapidly: in a neutral or slightly acid medium, on the contrary the phenomenon is slower. The case of epinephrine has been studied in detail by Schou and co-workers.[41] They have shown the essential roles of *p*H and temperature and indicated precisely the conditions under which optically active epinephrine may be stored. This is

a very important point, because the physiological activity of the levorotatory derivative is much greater than that of the racemic. Although it is only a matter of isomerization, from the standpoint of activity, this alteration is equivalent to an important decrease in the concentration of the active principle.

Hyoscyamine

Due to the fact that the combination of a dextro optical isomer with its levo form gives rise to a molecular association with evolution of heat—the racemic—whose physical properties are different from that of the derivative, it must be noted that the system has a tendency to stabilize when racemization takes place. Therefore the optically active derivative must be considered as "metastable." Its major tendency is toward racemization. Hyoscyamine has given rise to a recent and very interesting work on this subject.[42] It is known that in solution in absolute alcohol, this base is relatively stable, even when the temperature rose appreciably above 20°. This work shows that when alcohols of various nature are used, the more the electrical moment of the solvent increases, the more the speed of racemization increases, even in a neutral medium. But if the alcohols contain water, the rate of isomerization immediately increases considerably and the authors attribute this fact to the high electrical moment of the molecule. In their opinion, nonpolar or weakly polar solvents would permit preservation of optically organic molecules. Attention must also be given to the polarity of the active derivative itself. It has been noted, in fact, that alkaloids—which are strong bases—undergo racemization faster than those considered as weak bases: scopolamine in anhydrous alcoholic solution is easy to preserve. This work is interesting because it furnishes a rare indication in pharmacy of the possible role of solvents and their polarity; up to now we were accustomed only to the idea of their role in favoring ionization of molecules.

Lyophilization

Let us now say a few words about lyophilization. The ever growing importance of this technique in pharmacy is well known. In many cases, the best way to obtain and preserve a fragile substance in a dry state and, still more, a mixture of substances, is to freeze the solution and vaporize the solvent under reduced pressure, in order to desiccate afterwards under a vacuum. In this way we obtain a very light porous cake which may be preserved indefinitely in vacuum sealed ampuls, with the advantage of producing a solution in a minimum period of time because of the large surface of the solid with the solvent. It is with regard to the preparation of dry plasma in American industry that the first studies were carried out concerning the possible alterations of organic compounds. It was shown that they were practically nonexistent[43] and, moreover, that this desiccation process was the only one capable of sparing totally the solutes. In the case of dry plasma it has been shown, for example, that the electrophoresis diagram of proteins and lipoproteins was unaltered by lyophilization followed by solution. When it is known to what extent the slightest physical treatments are sufficient to modify the diagram, then we have the complete guarantee of security afforded by lyophilization. This guarantee of nonalteration has been confirmed in all cases where the experiment was carried out on other solutions.

Distillation

We have said a few words previously about distillation indicating that, when practiced at a sufficiently high temperature, it had the inconvenience of facilitating oxidation-polymerization in a large number of cases and especially with terpene mixtures. It is interesting to mention that obviously this risk may be reduced when the temperature is decreased by operating under reduced pressure, and further reduced when effected at low pressure with a pure nitrogen flowing intake (free from oxygen by passage over red copper) or, still better, with an hydrogen one. But modern industry tends to generalize the use of molecular distillation, where, in the absence of boiling, a simple vaporization of the liquid takes place, an operation which may give rise to fractionation, just as distillation itself. It is required that the liquid be previously free from gas—which is an extra guarantee that the operation will take place under perfect vacuum, that is, free from oxidation. But it must be noted that even careful distillations at low temperature do not permit avoidance of formation of extremely small quantities of polymers, as we note in the case of Raman spectrography.[45] There we have to irradiate the organic liquid to be studied with a monochromatic light source, and the light diffused laterally by the liquid is received in a spectrograph. When the liquid contains traces of polymerized impurities it gives rise simultaneously to a troublesome excess in diffusion and to some fluorescence, even more troublesome. It has been known for some time that the only way to overcome this inconvenience is to introduce the liquid to be studied in a U-shaped glass tube, obtain vacuum, and vacuum seal it subsequently. Following this operation, the empty extremity of the inverted U is placed in ice, the other branch being maintained at ordinary temperature. Very slowly, a vaporization-condensation takes place which, in a day or two, accumulates the distilled liquid in the cooled branch. This is the only way to obtain a sample free from polymers or fluorescence. Fortunately, the pharmaceutical industry does not require such a degree of purity.

A very frequent modern process which also gives rise to alterations is alumina or resin chromatography. We know how this purification process has been generalized. We must not forget that the substance on the column is distributed over a very large surface of adsorbent and that due to this fact is severely exposed to exterior aggressive agents. Experience shows, for example, that vanillin adsorbed on aluminum oxide is rapidly oxidized[46] and that it is very difficult to recover it in its original form when one operates "in the open." Any adsorption operation must therefore give rise to a serious control of the identity of the compounds thus fractionated.

Traces of Impurities

It may happen that the stability or instability of a given chemical compound, and particularly its photosensitivity, depend upon traces of impurity, even under the most unbelievable delicate conditions of operation.

Ferrand has had the occasion, in my laboratory,[47] to study the characteristic behavior of lead chloride. This salt, when prepared without any precaution at the crystalline state, possesses an intense yellow fluorescence. The same salt crystallized very slowly at ordinary temperature, in a Dewar dish for example, yields a product of the same chemical composition, entirely free from fluorescence. Finally, a very careful purification may lead to a nonfluorescent substance, which indicates that this property is due to an impurity. But we have systematically investigated the influence of all mineral ions we could imagine without identifying "the active ion." We had on hand a certain nitric acid, "pure," of industrial origin, which contained the active ion, to the extent that only a trace of this acid introduced in the solution where lead chloride crystallized, was sufficient to confer an intense fluorescence. This showed that fluorescence was due to an exterior chemical element and that, on the other hand, the crystallization procedure itself could increase fluorescence (rapid crystallization), decrease it (slow crystallization) or even suppress it (infinitely slow crystallization). Modern theories about the relationship between anomalies of the network and photosensitivity were thus verified, since lead chloride is very sensitive to light—with formation of reduced lead—but this sensitivity goes along with fluorescence. Nonfluorescent samples are rigorously stable to light. Nevertheless, it is always the question of an apparently pure substance yielding perfect results upon analysis. I have given this example only to show to what extent stability problems are closely related to problems of structure and purity.

Suspensions and Emulsions

I should still talk about complex systems such as suspensions and emulsions. But this would be the subject of a discussion in itself and I will be happy only to indicate that the physical causes of alterations which do occur in these systems seem to pose some difficult problems of surface physics. It is known that in the case of emulsions, the stability of the system is assured when the interfacial film has the structure of a "gel" or "solid" film because these practically oppose "coalescence." But such systems are generally indefinitely stable, under the strict condition that they will not suffer mechanical treatment. If agitation takes place and, moreover, if in order to homogenize the dispersion they are run through a mechanical crushing apparatus, the films are torn and the emulsion is destroyed.

In the case of suspensions of insoluble crystals in water, the difficulty is that the factors which facilitate dispersion and retard sedimentation, such as the addition of carboxymethylcellulose, have the inconvenience to facilitate agglutination, following sedimentation. Then a mass forms, which is difficult to redisperse upon agitation. This is what has been called "caking" and the difficulty in formulating such preparations consists in allowing a slow sedimentation along with absence of agglutination. Each particle must remain hydrophilic on all of its surface and must not adhere to neighboring particles. Summing up, it is a problem which on a large scale reproduces that of thixotropy. It is of interest to more dispersed systems, where the "micelles," generally because they are elongated, have a tendency to agglomerate upon standing. The result of this thixotropy is an increase of the apparent viscosity, increase which may become considerable. Rheology is the name that has been given to the study of these variations in apparent viscosity and this is a whole chapter of physical chemistry. Let us note that spherocolloids, on the contrary, have a viscosity approximately independent of the concentration and are not susceptible to variations of this nature.

Coacervation

The last phenomenon to which I will refer is "coacervation,"[49,50] or separation into two layers of a solution originally homogeneous, following the presence of one or more colloids and of various substances in solution. This is what one might observe when a very hydrophilic salt, such as sodium sulfate in a high concentration, is added to a very concentrated solution of polyvinylpyrrolidone. The mixture of the two solutions does not lead to immiscibility[51] but, rather, to the separation of both layers. The upper layer, of oily appearance, is very viscous, being a concentrated aqueous solution of the polymer. Separations of this type may occur in the course of the storage of pharmaceutical formulas, and it is good to be aware of their possibilities. The remedy is to make

use of ions with very little hydrophilic nature. Analogous phenomena correspond to the several cases of "demixing," known for some time, but which are far from the scope of this presentation, except in the case where a liquid which constituted an homogeneous phase separates in two layers in the course of storage. When this happens it follows a change in temperature. Systems with two immiscible liquids generally give rise either to an homogeneous phase below a certain critical temperature and separation above. This critical temperature is strongly influenced by the solutes in the system. It is therefore possible for a pharmaceutical preparation containing an organic solvent and water with, moreover, substances in solution, to give rise to separation either when temperature drops significantly below ordinary temperature or when it rises above; but then by raising the temperature back to 20° C. homogeneity of the system is reestablished. A particular case is that where a solution contains several colloids of a different nature. Under certain conditions of temperature and concentration, it is possible for an exclusively aqueous solution of two polymers to give rise to separation. The phenomenon has been observed by Dobry[52] (1948) with cellulose polymers, polystyrenes, and polyvinyl acetates. It is not necessarily a matter of "coacervation" but rather of a related phenomenon, corresponding likely to a certain unequal hydrophilic power of the polymers present.

We will not go into any further details regarding alterations of medicaments constituting heterogeneous systems. The considerable development of modern emulsion formulas, suspensions and creams would lead us too far. Summing up, most of the problems we have just discussed here are related to the present trend in pharmaceutical technique. Medicaments of a more and more unstable nature are used in galenicals of a more and more complex nature and we wish to extend the stability of such preparations over even longer periods of time.

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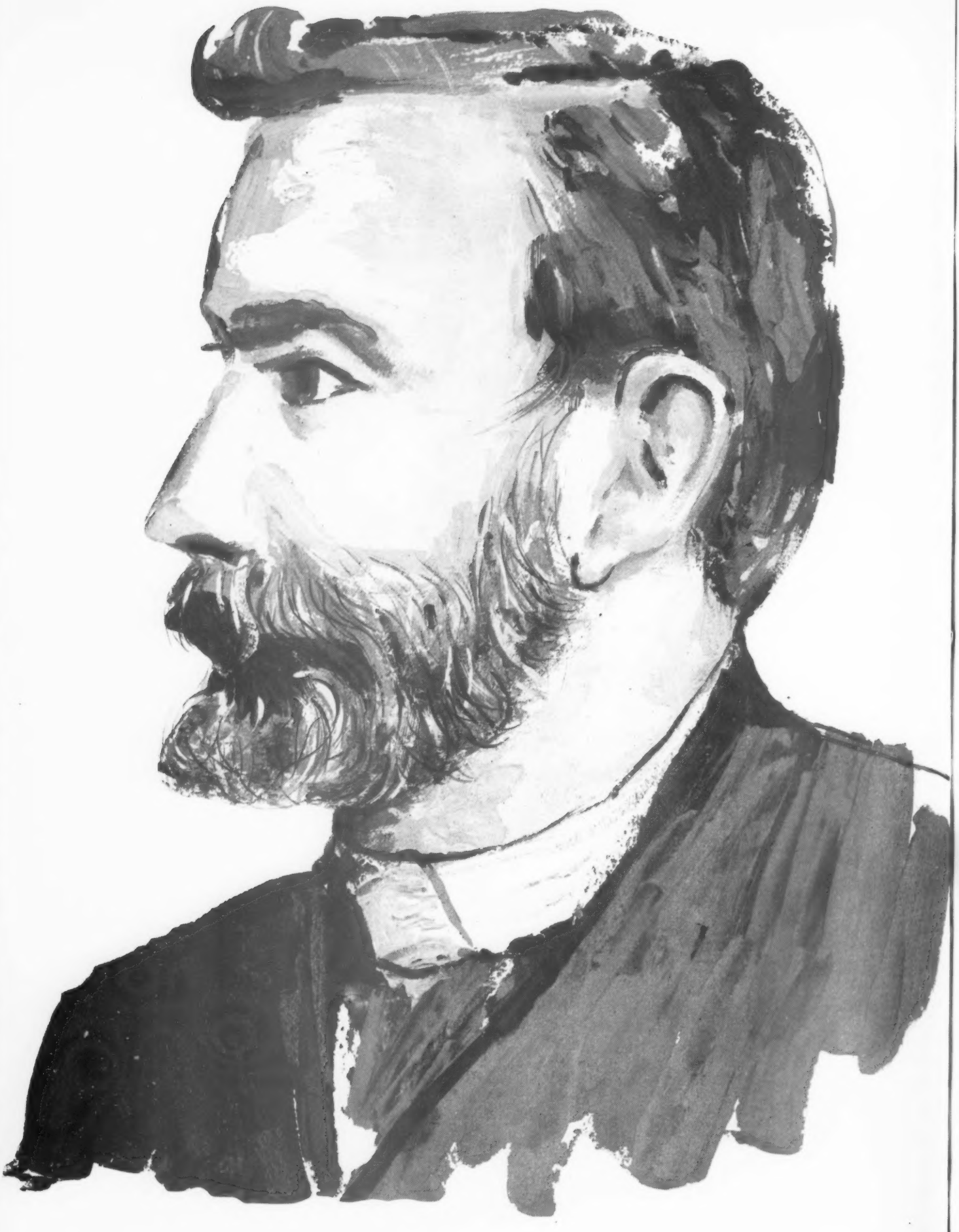

PAUL EHRLICH AND CHEMOTHERAPY

by GLENN SONNEDECKER

► JUST FIFTY YEARS AGO THIS SPRING Paul Ehrlich stood before the Congress for Internal Medicine at Wiesbaden, on the Rhine. He described the convincing accumulation of evidence for the effectiveness of "606" (arsphenamine) against syphilis; and he reviewed the conceptual basis of the underlying research that had brought chemotherapy into clinical practice. That same year, 1910, Ehrlich and S. Hata published their famous volume, "Die Chemotherapie der Spirillosen." During the last half of 1910 about 65,000 doses of arsphenamine (tradenamed Salvarsan) had gone across the world into the first widespread clinical trials; and Ehrlich's laboratories at Georg-Speyer Haus in Frankfurt am Main collaborated with the Hoechst Chemical Works nearby to begin the shift into large-scale production and distribution.[1]

The ovation accorded Ehrlich and his collaborators at the Congress at Wiesbaden echoed through the press of the world. Physicians and pharmacists, and laymen alike, acclaimed what had been achieved—and, as often happens, even more than had been achieved. The name *Paul Ehrlich,* and the term *chemotherapy* he coined, resounded with a new hope and protection for millions in every civilized country.

Meaning of Chemotherapy

No wonder that this culmination of a new way of research and of therapy seems worth remembering in pharmacy after half a century. While this series of events may be considered the beginning of the "era of chemotherapy," it is a bit paradoxical, yet logical, that we are no longer quite sure what chemotherapy means.

Ehrlich himself had in mind the use of chemicals to attack directly the pathologic organisms in the body, without doing unbearable harm to the host. The implied restriction to internal therapy has been modified by Alexander Fleming, and others, to include external or local chemotherapy. Now we hear antibiotic therapy called chemotherapy whether or not the antibiotics have a definite and known chemical structure.[2] More recently, the term likewise has been stretched to cover therapy that, while employing known chemicals, strikes against unknown etiologic organisms or mechanisms, as in "cancer chemotherapy."[3] Finally, by a logical extension that Ehrlich himself found conceivable,[4] those less fastidious may consider chemotherapy as any therapy with chemicals. Today this could mean any drug therapy, thus blurring all special meaning in the chemotherapeutic concept, and blurring the idea of a distinctive line of development.

The pharmacologists Arthur S. Loevenhart and W. K. Stratman-Thomas at the University of Wisconsin (1928), like others, saw the term as "somewhat difficult to define." They themselves restricted its scope to structure-activity relationships, a proposal never generally accepted. While they recognized that Ehrlich "used the term only in reference to infectious diseases," they felt "there is no reason why it should not include all types of substances used in therapeutics."[5]

Since common agreement on what we mean by "chemotherapy" seems to have been lost after fifty years of it, we use this occasion to propose for discussion another modified definition, intended to preserve the spirit of Ehrlich's approach, yet somewhat clarifying if not liberalizing the limits of the concept: "CHEMOTHERAPY" is a direct attack by chemicals of known structure, from whatever natural or synthetic source, upon a known pathogen, systemically or topically, without doing unbearable harm to the cells of the host."

It would seem to preserve a useful distinction if chemical drugs used in a different sense were termed more broadly as chemical therapy or drug therapy.

Putting chemistry in the service of medicine had been a zealous aim of the Paracelsians since the sixteenth century. But it was on new ground of modern science, with less speculative methods, that Ehrlich erected a cornerstone of therapy as today's pharmacist knows it.

Just as a therapeutic revolution evolved out of the half century just passed (sparked by Ehrlich as much as by any man), so the half century preceding him yielded new knowledge and methods of medical experiment that made possible the fertility of his own mind and work. This was the time, it will be recalled, of Claude Bernard, Rudolf Virchow, Louis Pasteur, Robert Koch, and Joseph Lister. Fritz Schaudinn,

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with Erich Hoffmann, discovered (1905) the syphilis spirochete, against which Ehrlich would try to launch a "magic bullet."

"Magic Bullet"?

By "magic bullet" is meant the idea Ehrlich ordinarily referred to as *therapia sterilisans magna*. In a single therapeutic blow, one dose, the body would be swept clean of infecting organisms. Ehrlich dreamed of this direct attack on pathogens in terms of his "side-chain theory," which hypothesized peripheral side-chains on living cells (suggested by analogy with Kekulé's side chains of the benzene ring). These could combine with food substances, or neutralize toxins.

Listen to Ehrlich himself tell how this imaginative idea applied to drug therapy: "I also wish to lay especial stress upon my view that the drugs, also, are attracted by and bound to the protoplasm molecule by certain atom groupings. I am inclined to look upon this as somewhat analogous to the binding of toxins and of similar proteid bodies. Yet on the other hand, there are fundamental differences between the two . . . I have now formed the opinion that in like manner [to the receptors that bind toxins to produce immunity, so] a part of the chemically defined substances is attached to the cell by groups corresponding to these receptors; these atom groupings I will distinguish from the toxin-receptors by the name of 'chemo-receptors' . . . . It is the arsenical radical as such, which is bound by the chemo-receptors . . . . The number of such chemo-receptors for poisons which a trypanosome cell posesses, represents the number of points of [chemotherapeutic] attack . . . . Every point of attack may, of course, be liable to be attacked by a host of different bodies, all of which have one specific [atom] group in common."[6]

However much present knowledge differs in detail, the lock-and-key concept of many therapeutic phenomena reminds us of Ehrlich's remarkable insight, which gave a strong impulse to research in several directions. Ehrlich began his own chemotherapeutic studies on arsenic compounds with atoxyl, which attracted his attention because of work by Uhlenhut and others.

By 1907, in a lecture at London, Ehrlich said "a basis has been gained on which we may hope successfully to undertake the practical attempt of suppressing sleeping-sickness. The exceedingly great difficulty of these studies is evidenced by the fact that hundreds and thousands of substances have to be examined by animals experiments, before a few producing a therapeutic effect can be found. I myself have in course of time examined more than 600 such substances."[7]

"606" Not Accidental

It was the 606th compound, Ehrlich later tells us, that proved to be an effective specific against syphilis, and related diseases, and inaugurated chemotherapy in the modern sense of the word. This single discovery has had tremendous consequence. Yet, Ehrlich himself already saw its wider significance as only the first fruit of a systematic way of work pregnant with promise. The introduction of "606," he repeatedly emphasized, "has been the result of very extensive purposeful synthetic work, and not an accidental discovery."[8]

Ehrlich was optimistic about the chemotherapeutic advances it portended in the years ahead.[9] So remained the Wisconsin pharmacologist, Professor A. S. Loevenhart, who in 1928 observed, "So great indeed have been the results of the cooperation of medicine and chemistry in this field [of syphilology] that the fighters against other diseases have been heartened and encouraged to follow the plan of campaign that was initiated by Ehrlich."[10]

Yet, the problem of extending specific chemotherapy proved to be far more intricate than had been foreseen. A quarter century after Ehrlich's greatest triumphs there had not yet been another major breakthrough. Then in 1935 came the first full report by Gerhard Domagk of the successful treatment of streptococcal infection in man with a sulfonamide (Prontosil), whose chemotherapeutic activity had been discovered in December 1932.[11] It is symptomatic of a persisting obstacle to chemotherapeutic progress that this father-compound of the "sulfa drug" era had been synthesized twenty-seven years earlier, even before Ehrlich announced the definitive work with arsphenamine.

Subsequently, the field of chemotherapy has unfolded in ways that might surprise even the imaginative mind of Paul Ehrlich, but that confirm the profoundness of his contribution and his influence.

The above article was originally published in the *Wisconsin Pharmacist* (July) 1960.

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Therapeutic Trends

edited by WILLIAM JOHNSON

Heparin Therapy In Autoimmune Hemolytic Anemia

Corticosteroids and splenectomy constitute the main forms of therapy in autoimmune hemolytic anemia. Large doses of a corticosteroids are given until the hemolytic process abates then a maintenence dose is given to control the disease. McFarland *et al.* report in *Blood 15*:741 (May) 1960 the use of heparin in controlling this disease. The trial showed that there was a sudden return to severe hemolysis after the discontinuation of heparin. One case was controlled for weeks by a single daily dose of 20 mg. The mechanism of action of heparin in autoimmune hemolytic anemia remains unknown. It does not appear to be due to any anticomplementary activity. Heparin should be tried more widely in autoimmune hemolytic anemia, particularly in situations in which response to corticosteroids and splenectomy has been disappointing.

RICHARD H. HARRISON

Amine Oxidase Inhibitors In Angina Pectoris

Isocarboxazid was administered to 27 patients with angina pectoris. Of the 23 patients who received the medication for 2 weeks or longer, the relief of pain was considered to be excellent in 11, good in 5, fair in 4, and failures in 3. Clinical side effects were reported by 13 patients. Except for orthostatic hypotension with syncope, these side effects were minor and did not necessitate interruption of treatment. There were no significant abnormalities in the laboratory findings. Pivalylbenzhydrazine was administered to 68 patients available for evaluation with this disorder. Sixty patients received the medication for 2 weeks or longer. The relief of the pain of angina pectoris was considered to be excellent in 21, good in 15, and fair in 9. There were 15 failures. No significant side effects were observed in either clinical or laboratory examination. W. Abrams *et al.*, reporting in *Am. J. Cardiol. 5*:634 (May) 1960, believe that these preliminary clinical studies warrant the following observations: 1. Some derivaties of iproiazid also possess antianginal properties; 2. There is no evidence at this time that the amine oxidase inhibitors interfere with the natural course of arteriosclerotic heart disease; and 3. The clinical effects in some patients are so marked it is believed that these compounds represent a significant advance in the management of patients with angina pectoris. Marplan and Tersavid used in this study were supplied by Hoffmann-LaRoche, Inc.

SYLVIA SCHMIDT

New Dental Chemotherapeutic Agent

In this experiment 3 percent aqueous hydrogen peroxide is compared with a stabilized solution of 3 percent urea peroxide in glycerin which has recently been described as being of interest in the treatment of oral lesions. The method used consisted of bringing the solutions in contact with thin blood films inoculated with *Staphyloccus aureus.* The results confirmed clinical observations that the good bactericidal action of 3 percent aqueous hydrogen peroxide, previously demonstrated *in vitro,* is lost almost immediately when the material is brought into contact with such films and that this is due to the rapid breakdown of the peroxide accompanied by the rapid evolution of oxygen caused by the enzymes present in the blood films. H. Cobe, in *Oral Surg. Oral Med., Oral Pathol. 13*:678 (June) 1960, points out that the preparation of urea peroxide in glycerin of comparable hydrogen peroxide content in the presence of such thin blood films broke down more slowly and retained the oxygen in contact with the blood as a compact foam. During an appreciable period, significant bactericidal action was demonstrated, especially where the glycerin solution was used undiluted or in minimum dilution. This solution was furnished by International Pharmaceutical Corp. as Gly-Oxide.

SYLVIA SCHMIDT

Transbuccal Pitocin

T. Dillon *et al.* in *Obstet. and Gynecol. 15*:587 (May) 1960 report that transbuccal Pitocin was administered to 100 patients for the induction and stimulation of labor. The method of administering the Pitocin linguet consists of placing a 100 U. tablet in the buccal space. The dosage is increased by adding 100 U. every 30 minutes until optimum uterine response is obtained. The tablets require about 1 hour to absorb. The medication is not swallowed. The patients were classified into 5 categories according to the status

of the cervix and the membranes. The percentage of successful induction for each category was high. Transbuccal Pitocin represents a technic of administration to be added to the established methods which, because of safety and ease of administration, may be preferable in the selected patient. Pitocin citrate linguets used in this study were supplied by Parke, Davis and Co.

SYLVIA SCHMIDT

A Series Of 2, 6, Distributed Phenoxyethyl Ammonium Bromides With True Sympatholytic Properties

A compound, TM-10, originally synthesized by Hey as a local anesthetic was found to possess some qualities as a sympatholytic agent. This study was to determine if a close analog of the original compound may retain its sympatholytic properties but remove undesirable side effects. The major effect of the compound is a slowly developing but very long lasting inhibition of adrenergic nerve activity. McLean *et al.* synthesized *alpha* and *beta* methyl derivatives of compounds TM-10 and TM-25 and the results of the studies and comparisons of these compounds are reported in *J. Pharmacol. Exp. Therap. 129*:11 (May) 1960. The studies showed that the site of action is the terminal sympathetic nerve ending. Alpha methylation reduced the objectionable muscarine effect of the parent compound TM-10. The alpha substituted compounds are less active than the beta substituted congeners. It was found that the 2, 6, dimethyl compounds were more effective when given orally than their dichloro analogs. The beta substituted TM-10 seems worthy of human trials to determine if its unique type of sympatholytic activity may have a useful application in clinical hypertension and peripheral vascular disease.

RICHARD H. HARRISON

Synthetic Polyelectrolytes As Tumor Inhibitors

Anionic polysulfonates and polyphosphates have been shown to be potent inhibitors of transplanted tumors in mice. This study was done by Regelson *et al.* to determine if this tumor inhibition could be a function of the density and distribution of anionic charge within the polyelectrolyte molecule. Two classes of synthetic polymers were used in the study, polycarboxylates derived from ethylene-maleic anhydride copolymers and those derived from polyacrylic acid. For convenience in the ethylene-maleic acid group the hydrolysed form is abbreviated HEMA and the ammoniated is noted as AEMA. In most experiments sarcoma 180 was the tumor used. Solutions of the compounds to be tested were prepared in isotonic saline and stored in the cold. Dosage was 0.5 ml. of drug solution injected intraperitoneally daily beginning 24 hours after tumor innoculation. The drug was given for six days and the animals killed on the eighth day. The results of the tests, reported in *Nature 186*:778 (June 4) 1960, showed that at least one ionizable carboxyl group is required for the polymers to show significant tumor inhibition. Optimum activity was obtained in the series where carboxamide and ionizable carboxyl groups were interdispensed on the polymer backbone. The results of the tests seemed to support the hypothesis that tumor inhibition by polyelectrolytes may be a function of charge-density and distribution on the polyelectrolyte molecule.

RICHARD H. HARRISON

W-583—Report Of Antihypertensive Effectiveness

The sedative effects of W-583 (a propanediol dicarbamate) were recently evaluated in humans and the sedative-hypnotic abilities of the drug were confirmed in this study. Duarte *et al.* report the results of the use of this drug in *Current Therap. Research 2*:148 (May) 1960. The antihypertensive effectiveness of this compound was markedly potentiated by the simultaneous administration of hydrochlorothiazide. In a series of 19 patients, 11 obtained a significant blood pressure reduction in the supine position, and 12 achieved a significant orthostatic antihypertensive response. It was postulated that the tranquilizing properties of W-583 could account for the modest antihypertensive response which was obtained with the drug alone. However, animal studies have suggested that W-583 possesses additional specific antihypertensive action which probably warrants further clinical studies. No toxic effects were observed during the use of this drug.

WILLIAM E. JOHNSON

N-Ethylisatin b-Thiosemicarbazone—Chemotherapeutic Agent Active Against Smallpox Infection

In 1956, from those countries for which records are available, 60,431 cases of smallpox were reported with 31,622 deaths. A considerable number of derivatives of isatin b-thiosemicarbazone have been prepared and tested for antiviral activity, and some have been found to be considerably more active than the parent compound. In view of the activity of compounds of this type against two representatives of the pox virus group, it was of interest to see whether they would also have an effect in infections with smallpox virus. Bauer and Sadler report in *Lancet* I: 1110 (May 21) 1960 that infant mice infected intracerebrally with 100 LD_{50} of alastrim virus could be protected against death and the development of encephalitis by treatment with N-ethylisatin b-thiosemicarbazone at a dose level of 5 mg. per Kg. The compound has a low toxicity and the therapeutic index is greater than 2,000. The antiviral chemotherapeutic activity found in animal experiments is thus high enough to suggest that this compound may be of value in the specific treatment of smallpox in man.

WILLIAM E. JOHNSON

Timely Drugs

AquaMephyton

GENERIC NAME: Phytonadione (Vitamin K_1).

INDICATIONS: Prophylaxis and treatment of hemorrhagic disease of the newborn; to adjust prothrombin time before surgery or childbirth; hypoprothrombinemia due to various causes.

SIDE EFFECTS AND CONTRAINDICATIONS: Transient flushing sensations, 'peculiar' taste in mouth, dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dypsnea and cyanosis may occur, though rarely.

DOSAGE: For actual or imminent hemorrhage, 5 to 25 mg. intravenously; for potential but remote threat of hemorrhage, 1 to 25 mg. intramuscularly or subcutaneously.

PREPARATIONS: Colloidal solution containing in each ml.: vitamin K_1 10 mg., polyoxyethylated fatty acid derivative 70 mg., dextrose 37.5 mg., benzyl alcohol 9 mg., Water for Injection, to make 1 ml.

PACKAGING: Ampuls of 1 ml.

SUPPLIER: Merck Sharp & Dohme.

Brevital Sodium

GENERIC AND CHEMICAL NAMES: Methohexital sodium; sodium *a-dl*-1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbiturate.

INDICATIONS: Intravenous barbiturate anesthetic for use in reduction of fractures, before electroconvulsive therapy, in certain genitourinary and gynecologic examinations, and in oral surgery. Also recommended in prolonged anesthesia, alone or in conjunction with gas or vapor inhalant anesthetics.

SIDE EFFECTS AND CONTRAINDICATIONS: Only those applying to any general anesthetic, i.e., traumatic shock or severe heart condition.

DOSAGE: Because of increased potency, slower rate of infusion is required in induction dose than with other barbiturate anesthetics. For detailed dosage, see package literature.

PREPARATIONS: Ampuls containing 0.5 Gm. or 2.5 Gm. methohexital sodium, with anhydrous sodium carbonate, in crystalline form.

PACKAGING: Boxes of 1 and 25 ampuls.

SUPPLIER: Eli Lilly and Co.

Medrol Acetate, Veriderm
Neo-Medrol Acetate, Veriderm

COMPOSITION: Methylprednisolone and neomycin, in lipid base.

INDICATIONS: Where topical treatment of skin lesions with adrenocortical steroids, with or without antibiotic, is indicated.

DOSAGE: After careful cleansing of skin, initial application may be made 1 to 3 times daily.

PREPARATIONS: Medrol Acetate Veriderm—methylprednisolone 0.25% or 1%, with methylparaben and butyl-p-hydroxybenzoate; Neo-Medrol Acetate Veriderm—methylprednisolone 0.25% or 1% with neomycin sulfate 5 mg./Gm., and methylparaben and butyl-p-hydroxybenzoate.

PACKAGING: Tubes containing 5 Gm.

SUPPLIER: Upjohn Co.

Prelu-Vite

COMPOSITION: Phenmetrazine (Preludin) hydrochloride, vitamins A, D, B_1, B_2, B_6, B_{12} and C, niacinamide, calcium pantothenate, iron, calcium, phosphorus, iodine, and copper.

INDICATIONS: Where administration of vitamins and minerals is desired in combination with an appetite-suppressant for control of obesity.

SIDE EFFECTS AND CONTRAINDICATIONS: Should not be administered to patients with severe hypertension, thyrotoxicosis or acute coronary disease.

DOSAGE: One capsule 2 or 3 times daily.

PREPARATIONS: Capsules containing phenmetrazine hydrochloride 25 mg., together with vitamins and minerals.

PACKAGING: Bottles of 100 capsules.

SUPPLIER: Geigy Pharmaceuticals.

Robaxisal-PH

COMPOSITION: Methocarbamol (Robaxin), phenacetin, acetylsalicylic acid, hyoscyamine sulfate, and phenobarbital.

INDICATIONS: For relief of primary pain, relaxation of spasm of voluntary muscles and associated pain and discomfort, and for relief of pain due to arthritis, pain in the back, myositis, as well as pain associated with or due to spasm of skeletal muscle.

SIDE EFFECTS AND CONTRAINDICATIONS: Known or suspected personal allergy, sensitivity or idiosyncrasy to phenobarbital, acetylsalicylic acid; minor side effects such as lightheadedness, dizziness and mild nausea may occur rarely.

DOSAGE: Two tablets 4 times daily in adults.

PREPARATION: Tablets containing methocarbamol 400 mg., phenacetin 97 mg., acetylsalicylic acid 91 mg., hyoscyamine sulfate 0.016 mg., and phenobarbital 8.1 mg.

PACKAGING: Bottles of 100 and 500 tablets.

SUPPLIER: A. H. Robins Co.

Sorboquel

COMPOSITION: Polycarbophil and thihexinol methylbromide.

INDICATIONS: Symptomatic treatment of chronic and acute diarrhea.

SIDE EFFECTS AND CONTRAINDICATIONS: Infrequent and usually mild atropine-like effects. Contraindicated in patients with glaucoma; should be used with caution in patients with pyloric stenosis or intestinal strictures, or in whom tachycardia might prove harmful.

DOSAGE: Adults, one tablet 4 times daily. Dosages exceeding 6 tablets daily should not be used over prolonged periods.

PREPARATIONS: Tablets containing 0.5 Gm. polycarbophil and 15 mg. thihexinol methylbromide.

PACKAGING: Bottles of 50 and 250 tablets.

SUPPLIER: White Laboratories.

HIGHLIGHTS OF THE 1960 ANNUAL MEETING

► MEMBERS OF THE AMERICAN SOCIETY OF HOSPITAL PHARMACISTS met for their seventeenth Annual Meeting in Washington, D. C. during the week of August 14. Meetings were held in conjunction with the Convention of the parent organization, the American Pharmaceutical Association. Under a new plan followed this year, meetings were held throughout the week with the A.Ph.A. General Sessions and House of Delegates being held at alternate times from the sessions of the affiliated organizations. The ASHP House of Delegates met on Sunday afternoon and again on Thursday morning. General sessions were held on Monday afternoon, Tuesday morning, Wednesday afternoon, and Thursday morning. Those attending the convention therefore had a better opportunity to participate in the total convention activities, view the exhibits, and attend the various special events and entertainments.

To bring to the membership highlights of the ASHP meetings and make available the papers presented and the official reports will require several months. However, here we are presenting a pictorial review and a brief summary of activities. The resolutions adopted at this Annual Meeting constitute the SOCIETY's official actions and these appear on page 565. The complete proceedings, including a report of the meeting and the various officer and committee reports, will make up a special section in the November issue of the JOURNAL. When feasible, all papers presented at the Annual

ASHP Officers for the 1960-1961 term. Shown in the photo left to right are Sister Mary Berenice, S.S.M., Treasurer; Peter Solyom, Vice-President; Clifton J. Latiolais, President; and Joseph Oddis, Secretary

A Session of the ASHP House of Delegates

Meeting will be published and special attention is being given to printing those papers of timely interest at an early date. The business sessions of the 1960 Annual Meeting were ably presided over by President Vernon O. Trygstad who, at the end of the meeting, had completed a most successful year as the sixteenth president of the ASHP.

An outstanding program was arranged by the Society's Committee on Program and Public Relations under the chairmanship of Mr. Clifton J. Latiolais.

Many aspects of the A.Ph.A. program were of high interest to hospital pharmacists. Participation and attendance at the Association's General Sessions, House of Delegates and Sections provided a wide background of professional activities. Of particular note to the hospital pharmacists was a live television broadcast from the Clinical Center of the National Institutes of Health, Bethesda, Maryland. This was moderated by Mr. Milton Skolaut, Director of Pharmacy Service at the Center. Also, noteworthy was the seminar on generic name prescribing and dispensing following the theme "What's In a Name?" This is to mention but a few of the many discussions and papers presented at the meetings throughout the week.

Local cooperation and helpfulness were evident throughout the meeting. Members of the Maryland Association of Hospital Pharmacists headed by their president, Robert Statler, handled much of the details in arranging for special events and serving as hosts for the Society Suite.

The local Committee also assisted with plans for the traditional ASHP breakfast on Thursday morning. Presided over by President-Elect Clifton Latiolais, the breakfast carried out the tradition of informality and fun.

Hospital pharmacy was represented among the exhibits with a display depicting activities of the ASHP and the Division, including the *American Hospital Formulary Service.*

President Trygstad makes a presentation to Gloria Francke who served as Secretary of the Society for the past eleven years

Mr. Thomas Foster, recipient of the 1960 H.A.K. Whitney Award, receives plaque from Mrs. Jane Rogan, President of the Michigan Society of Hospital Pharmacists

House of Delegates

Forty-four of the SOCIETY's 54 affiliated chapters were represented by 46 delegates in the House of Delegates. Other members of the House included eight members of the Executive Committee, and eight chairmen of Special Committees making a total of 62 voting delegates. Also represented by fraternal delegates were the various branches of the government services including the Department of Army, the Department of the Air Force, the Department of the Navy, the U.S. Public Health Service and the Veterans Administration.

Representatives of the Catholic Hospital Association and the American Hospital Association also participated in the meetings. At the first General Session Dr. Madison Brown brought greetings on behalf of the A.H.A., Dean Howard C. Newton for the A.Ph.A., and Mr. John James for the C.H.A.

The House of Delegates, meeting for the eleventh year, constituted an effective body in bringing before the group major problems affecting hospital pharmacy practice and local organizations. With representatives from throughout the country and from a large percentage of the ASHP affiliated chapters, the group exhibited high interest in all aspects of SOCIETY activity.

In a panel discussion on "Preliminary Proposals of the ASHP Committee on Reorganization," Mr. Walter Frazier, Chairman of the Committee, presented proposals for changes in the SOCIETY's organization and management, covering the executive body, makeup and functions of the House of Delegates and election of officers and those who constitute the executive group. Questions and comments were made by members of the panel and audience. It was emphasized that the proposals are *preliminary* and members and affiliated chapters will have an opportunity to study them and make further recommendations.

Election of Secretary

In a special report to the House of Delegates at the opening session on Sunday, Secretary Gloria Francke presented a formal resignation on her behalf. She then presented the Executive Committee's nomination of Mr. Joseph Oddis for the Office of Secretary and moved his election which was unanimously approved by the House.

Concluding this historical occasion in the SOCIETY, tributes on behalf of the membership were presented by Sister Mary Berenice, who has served as treasurer and a member of the Executive Committee for a number of years, and by Mr. Grover C. Bowles, a past president. Also, presentation of a gift to Mrs. Francke was made by President Trygstad. A large reception for members and friends of the Society was held in honor of the retiring secretary immediately following the House of Delegates.

Whitney Award Lecture

Hospital pharmacy's highest award was presented to Mr. Thomas A. Foster at a dinner honoring the recipient on Monday night. With Mr. Leo Godley serving as toastmaster, greetings and tributes were presented by Dr. Don Francke for the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, Dr. William S. Apple for the American Pharmaceutical Association, and Mr. Alanson Willcox for the American Hospital Association.

On presenting the plaque commemorating the occasion, Mrs. Jane Rogan, President of the Michigan Society, praised Mr. Foster's contributions to hospital pharmacy and to the profession. Responding, Mr. Foster gave the 1960 H.A.K. Whitney Lecture Award entitled "The Expanding Role of the Hospital Pharmacist as a Member of the Health Team." In this address, he urged hospital pharmacists to view their "expanding roles" and look forward to future accomplishments. He praised the work of the SOCIETY pointing out the challenges ahead and concluding with the prediction that hospital pharmacists will, in the coming decades, recreate in the minds of the American people the thought that "pharmacy is truly a health profession."

Miss Adela Schneider receives award for outstanding work in membership activities from Chairman of the ASHP Committee on Membership and Organization Louis P. Jeffrey

ACA and ASHP Joint Meeting

A joint meeting of the American College of Apothecaries and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS drew a large attendance and offered an opportunity to hear speakers on subjects of mutual interest, as well as to discuss areas of dissent.

In a paper on "New Therapeutic Agents and How to Evaluate Them," Dr. Herbert S. Kupperman of the New York University Postgraduate Medical School, warned pharmacists regarding possible over-enthusiasm of those concerned with promoting drugs and perhaps even that of the researcher. He suggested careful evaluation of the findings of investigators, giving examples of results which can be misinterpreted and the paramount importance of always considering effects on humans since animal studies may not *always* give the same therapeutic response.

A discussion of "Social Forces Affecting Hospitals and Hospital Pharmacy," coupled with a panel on "Trends Affecting Retail and Hospital Pharmacy Practice," opened areas of controversy between the two specialties. Mr. Ray Brown, Superintendent of the University of Chicago Clinics, Chicago, described the hospital as the pooled resources of the community for medical care. He stated that what is happening in hospital pharmacy serves as a criteria of what is happening in the total hospital. He predicted that the volume of drugs dispensed in hospitals would increase by 29 percent by 1975, simply due to the population increase and ignoring other factors. The latter will, however, cause increased utilization of hospitals

Director of the American Institute of the History of Pharmacy, Glenn Sonnedecker, presents awards to Sister Fernande-Marie and Captain James Stover

and further increase the volume of drugs dispensed. These include the rise in the general economic and educational status of the population, the increased percentage of older people, the number of working wives and new methods of treatment and prevention of disease. Mr. Brown further predicted an increase in drug inventory with the development of more specialty drugs for a large number of more complex illnesses and increased use of outpatient service as the result of the hospital becoming a center for all medical care services.

Participating in the panel, Mr. Leonard Tibbetts of Arlington, Massachusetts and Mr. Frank Kunkel of Cincinnati, spoke for the ACA. The ASHP was represented by Mr. Grover C. Bowles of Memphis, Tennessee, along with Dr. Brown. Opening the discussion with a paper, Mr. Tibbetts pointed out areas of dissent—particularly dispensing to outpatients and "substitution" in hospital pharmacy—suggesting that such practices had been forced on hospital pharmacy by hospital administration and boards of trustees. Mr. Bowles and Mr. Brown, speaking extemporaneously, pointed out with emphasis that this is not the case and referred to Mr. Brown's comments made earlier in the session. Mr. Kunkel asked for consideration of areas in which the two groups—the ACA and the ASHP—could cooperate, pointing out the needs for pharmaceutical service in small hospitals and suggesting a Joint Committee of the two organizations. This session which also offered opportunity for audience participation was presided over by ACA Secretary Robert Abrams.

Significant Events and Actions

Since it is not possible to give a full report of the week's activities, the following is to summarize significant events and actions taken at the 1960 Annual Meeting of the ASHP:

•Approved a change in the ASHP Constitution, providing for a category of membership for hospital pharmacists in organizational work, who retire, and who are temporarily unemployed. (This proposed change will be sent to the membership for vote by mail ballot.)

•Approved changes in ASHP By-Laws discontinuing the Committee on Pharmacists in Government Services and establishing a new standing Committee—the Committee on Resolutions.

•Elected three Honorary Members of the Society—*Sister Mary Ludmilla,* St. Mary's Hospital, St. Louis, Missouri, the first treasurer of the Society; *Hans S. Hansen,* St. Agnes Hospital, Fresno, California, president of the ASHP for the 1946-1947 term; and *Albert P. Lauve,* Mercy Hospital, New Orleans, Louisiana, an ASHP charter member who has contributed much in the early activities of the Society.

Honorary members in the Society are elected on the unanimous recommendation of the Executive Committee and approval of the membership at the Annual Meeting. Citations presented when electing the above members will be published at a later date.

•Named Gloria Niemeyer Francke, Secretary of the ASHP 1949-1960, a Member of the Society for Life.

•Presented awards to Captain James W. Stover, Washington, D. C., and to Sister Fernande-Marie, Ottawa, Canada, for writing on subjects related to the historical aspects of hospital pharmacy. The presentation, made by Dr. Glenn Sonnedecker, Director of the American Institute of the History of Pharmacy, is an annual event based on competition sponsored by the ASHP Committee on Historical Records in cooperation with the AIHP.

•Honored Miss Adela Schneider, Houston, Texas, for outstanding work in recruiting members for the A.Ph.A. and ASHP. An award was made by Mr. Louis Jeffrey, Chairman of the Society's Committee on Membership and Organization, and included a three year membership in the ASHP and a three-year complimentary registration at the A.Ph.A. conventions. At the same time, Mr. Jeffrey named the following individuals for honorable mention in connection with their contributions to the membership work of the Society: Franklin Cooper, District of Columbia; Clifton J. Latiolais, Ohio; Dell Olszewski, Wisconsin; Sister M. Gonzales, R.S.M., Pennsylvania; Sister M. Teresa, Oklahoma; Sister Mary Maurice Flynn, Georgia; and Theodore Taniguchi, Washington State.

•Heard A.Ph.A. Secretary Dr. William Apple speak on "Mutual Responsibilities for Professional Survival." Dr. Apple stressed our role to "serve our fellow citizens rather than ourselves," and pointed out the need to apply ourselves to the future in our philosophy of service. He asked that we not lag behind, but rise to the occasion of the changes in the medical care field. Dr. Apple also brought to the House of Delegates significant comments regarding current issues in the pharmacy profession.

•Heard a panel discussion on the "Guiding Principles in the Operation of the Hospital Formulary System" as promulgated by the Joint Committee of the AHA and ASHP. This, along with a paper on the "Legal Aspects of the Formulary System in Hospitals" by Mr. Alanson Willcox, offered opportunity for thorough exploration of the formulary system. Mr. Willcox, General Counsel for the American Hospital Association's Washington Bureau, has given much attention to this important subject and presented to hospital pharmacists the legal interpretations helpful in application of the system.

•Received a report on the status of the ASHP Formulary Service by Director William M. Heller. In noting a year of progress for the Formulary Service, Dr. Heller reported that more than 9,000 subscriptions are in effect and outlined plans for future monographs and supplements.

•Listened to reports from officers and committee chairmen, concluded by the Address of President Trygstad. Highlights of his address pointed to the Society's role in interprofessional cooperation. Also, he called attention to Project HOPE and recommended cooperation.

•Enjoyed numerous papers on professional and scientific subjects by hospital pharmacists, educators, and members of allied health fields.

•Received with approval action of the ASHP Executive Committee regarding the Pennsylvania State Board's proposed regulations covering the licensing and operation of hospital pharmacies. On request from an affiliated chapter, as well as recommendations from individual members, the ASHP Executive Committee, after due consideration and in the belief that such rulings affect the total profession, ask Dr. William Apple for A.Ph.A. consideration of the matter. In a subsequent communication, Dr. Apple related that the A.Ph.A. Council is asking for a meeting of the Board with representatives of the A.Ph.A., the ASHP, the National Association of

Boards of Pharmacy and the Pennsylvania Pharmaceutical Association. At the close of the meeting, action on the A.Ph.A.'s request was pending and the membership in attendance was informed accordingly.

•Heard proposals from the President-Elect Clifton J. Latiolais regarding future plans for SOCIETY action. Among significant new activities during the coming year will be a study of means of providing pharmacy service in nursing homes, appointment of a Committee on Professional Ethics, review of the *Outline for a Course in Hospital Pharmacy Administration* which was originally developed in 1951, along with continuation of current activities and maintaining liaison with numerous related organizations.

New Officers and Nominees

At the final General Session on Thursday, President Trygstad installed the new officers to serve during the 1960-1961 term. Mr. Clifton J. Latiolais, Director of Pharmacy Service at the Ohio State University Health Center, Columbus, Ohio, became president. Serving with him as Vice-President is Mr. Peter Solyom, University of Chicago Clinics, Chicago, Illinois. The new Secretary, Mr. Joseph Oddis, whose term began at the end of the 1960 Annual Meeting, was installed and will serve in a dual capacity as Director of the Division of Hospital Pharmacy and ASHP Secretary. Sister Mary Berenice, S.S.M., continues to serve a three-year term as treasurer. Other members of the new Executive Committee are listed on page 2 of this issue of the JOURNAL.

Nominations for officers of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS for the 1961-1962 term as follows:

For President: Jack S. Heard, San Francisco, California, and Louis P. Jeffrey, Albany New York.

For Vice-President: Terry Nichols, Atlanta, Georgia, and Gerard Wolf, Pittsburgh, Pennsylvania.

Ballots for the election of the President and Vice-President and for the vote on the proposed change in the Constitution will be sent to all Active Members of the SOCIETY within sixty days following the nomination.

. . . resolutions

passed at 1960 Annual Meeting

Actions taken at the Annual Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS *are the result of recommendations of its officers, committees, and delegates from Affiliated Chapters, and are expressed in the form of resolutions.*

The resolutions submitted by the various groups were considered by the Committee on Resolutions under the chairmanship of Mr. Robert Lantos, and including the following additional members: Mr. Peter Solyom, Mr. Jack Heard, and Mr. Terry Nichols. Also serving as assistants to the Committee were the following: Mr. Herbert Riemen, Mr. George Provost, and Mr. Theodore Taniguchi.

The resolutions were presented to the membership at the Annual Meeting and voted upon. Those resolutions finally adopted are presented here.

1

Amendment of the Constitution

WHEREAS the SOCIETY'S Constitution (Article I, Section 3) does not specifically categorize hospital pharmacists who are in hospital pharmacy organizational work, who retire, and who are temporarily unemployed, and

WHEREAS these members have been, or still are active members of the SOCIETY but are not currently practicing pharmacy in hospitals, now therefore be it

RESOLVED that Article I Section 3 of the Constitution be amended by the addition of the following sentence:

"Those hospital pharmacists engaged in organizational work in hospital pharmacy, and those who have retired from hospital pharmacy practice, or are temporarily unemployed may be classified as active members by action of the Executive Committee upon request of the member concerned."

In accordance with the provision for amending the Constitution, the above will be submitted to the membership for vote by mail ballot.

2

Amendment of By-Laws—Standing Committee Discontinued

WHEREAS in Chapter VI, Article 5, of the SOCIETY'S By-Laws, the Committee on Pharmacists in Government Service is a Standing Committee of the ASHP, and

WHEREAS the work of the Committee on Pharmacists in Government Service of the ASHP is duplicated by the Committee on the Status of Pharmacists in Government Service of the American Pharmaceutical Association, now therefore be it

RESOLVED that the Committee on Pharmacists in Government Service of the ASHP be discontinued as a Standing Committee.

Resolution Number 2 was adopted and will be incorporated in the By-Laws.

3

Amendment of By-Laws—Standing Committee Established

WHEREAS the Committee on Resolutions has played a highly important role in the affairs of the SOCIETY, and

WHEREAS the Chairman of the Committee must be constantly aware of the deliberations of the Executive Committee throughout the entire year, and

WHEREAS deletion of the Committee on Pharmacists in Government Service reduces the membership of the Executive Committee, now therefore be it

RESOLVED that the Committee on Resolutions be established as a Standing Committee of the SOCIETY, and be it further

RESOLVED, that Chapter VI, Article 5 of the By-Laws be changed to read,

"Committee on Resolutions shall be responsible for (1) drafting statements in resolution form which shall reflect the official policy of the SOCIETY, (2) reviewing the recommendations made in the address and reports of the Officers, Standing and Special Committees and the Executive Committee at the Annual Meeting and to prepare appropriate resolutions which require membership approval, (3) reviewing resolutions submitted to it from affiliated chapters and from individual members of the Society; conferring with the parties concerned whenever necessary about the intent or any other aspect of the report, and submit recommendations at the final general session of the Annual Meeting. It shall also establish a functional system of indexing all SOCIETY resolutions and maintaining the system by including any subsequent SOCIETY resolutions."

Resolutions Number 3 was adopted and will be incorporated in the By-Laws.

4

Outpatient Service

WHEREAS ministering to the needs of the sick has always been a matter both for charitable endeavor and for economic gain, and

WHEREAS members of the public health professions have traditionally ministered to both prince and pauper, and

WHEREAS people of all economic strata utilize the facilities and services of the modern hospital, of which the pharmacy and its pharmacist are, and must remain, integral and inseparable parts, and

WHEREAS it is inevitable that, due to the complexities of modern medical care, all members of the health professions serving in hospitals will be called upon to play an increasingly important role in ministering to the health needs of the people, working through the organized hospital wherein each profession must fulfill its destiny, be it therefore

RESOLVED that the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, in annual convention assembled, asserts and believes that hospital pharmacists have unquestionable and unchallengeable moral, legal and ethical rights to serve patients, both indigent and non-indigent, by filling prescriptions written by members of the hospital's medical staff for outpatients.

5

Overseas Pharmacy Exhibits

WHEREAS American-sponsored drug store exhibits at oversea fairs, such as those held in Belgium, Poland and Yugoslavia, have not been typical of American pharmacy, much less showing pharmacy at its best, and

WHEREAS these exhibits have been a source of embarrassment to professional pharmacists in America and repugnant to the professional spirit prevailing in European countries, and

WHEREAS exhibits of the caliber cited serve no useful purpose contributing neither to American pharmacy nor to pharmacy overseas, therefore be it

RESOLVED that government and private agencies be requested not to defile the professional and scientific contributions of American pharmacy nor subject pharmacy to misrepresentation or ridicule by fostering any overseas exhibit in an unprofessional environment or of an unprofessional character, and be it further

RESOLVED that a copy of this resolution be sent to the Department of State and to the Department of Commerce.

6

Project Hope

WHEREAS Project HOPE is one of the most imaginative, privately sponsored projects yet devised to carry to the newly developed countries the medical knowledge and skills they so sorely need, and

WHEREAS Project HOPE needs the services of two or more well qualified pharmacists to serve as practitioners and teachers and to form an integral part of its health team, therefore be it

RESOLVED that the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS pledge its moral and financial support to Project HOPE and call upon other professional pharmaceutical organizations to join with the SOCIETY in offering assistance in the selection of pharmacists for the project and in making a financial contribution toward the support of these pharmacists.

7

Liaison Committee

WHEREAS the Board of Trustees of the American Hospital Association voted,

"To urge state hospital associations and state hospital pharmacy societies to establish liaison committees to consider all matters of mutual interest and concern; further

"To suggest to secretaries of state hospital associations and state hospital pharmacy societies that a careful examination be made of laws which regulate the operation of hospital pharmacies in their respective states, and of rules and regulations of the state board of pharmacy or other appropriate agencies, and further,

"To encourage liaison committees of hospital administrators and hospital pharmacists to establish cooperative and friendly relationships and suitable means of communication with the state board of pharmacy or other appropriate agencies, if deemed necessary," and

WHEREAS the Executive Committee of the SOCIETY, recognizing the significance and value of such liaison, approved these recommendations; now therefore be it

RESOLVED that these recommendations be transmitted to all the Affiliated Chapters with the request that they lend their support and cooperation toward implementing of these suggested recommendations.

8

Appreciation To Paul F. Parker

WHEREAS Paul F. Parker has exhibited vigorous leadership in his accomplishments as immediate past Director of the Division of Hospital Pharmacy, therefore be it

RESOLVED that the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS extend a rising vote of thanks to Paul Parker and wish him the best of success in his new assignment.

9

Appreciation To Organizations

RESOLVED that the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS express its sincere appreciation to

The American Pharmaceutical Association, and the Division of Hospital Pharmacy for their valuable assistance to hospital pharmacy and to the SOCIETY during the past year;

The American Hospital Association and its Council on Professional Practice for their effective cooperation in furthering better hospital pharmacy practice;

The Catholic Hospital Association and its Committee on Pharmacy Practice, for the activities of the Association in promoting better pharmacy practice.

10

Appreciation to Committees and Individuals Responsible for Annual Meeting

RESOLVED that the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS express its sincere thanks and heartfelt appreciation to all the thoughtful individuals, committees, and organizations who extended to the SOCIETY's members and guests the excellent program arrangements, the many fine services, accommodations, and entertainment features of this Seventeenth Annual Meeting held in Washington, D. C.

11

Appreciation To Dr. William S. Apple

WHEREAS Dr. William S. Apple has demonstrated outstanding administrative skill and leadership in the interest of all of Pharmacy during his first full year as Secretary of the American Pharmaceutical Association, and

WHEREAS achievements for the profession of Pharmacy benefit all of its segments and specialties, be it

RESOLVED that the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS commend Dr. Apple, express confidence in his leadership, and pledge its continuing support.

12

Tribute to Gloria Niemeyer Francke

▶ WHEN STRONGLY MOTIVATED INDIVIDUALS band themselves together for the purpose of achieving worthwhile objectives, they succeed almost in direct proportion to the qualifications of their selected leaders.

Hospital pharmacists, as a class, have achieved an enviable reputation for good planning, hard work, courage, self-sacrifice, faith, foresight, sound judgment and devoted service in their efforts to create a SOCIETY to represent them actively in professional and public affairs.

This has not come about by accident. Nor is it the strong arm of a dictator or the machinations of a master-mind which are responsible for the unprecedented success that has crowned the efforts of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS.

Its steady growth in numbers, in influence, and in prestige has been due to the high quality of its leadership and to the willingness of the membership to trust in the democratic process for selecting its leaders.

The annually elected leaders of the SOCIETY have come and gone, each adding his or her contribution for the good of the whole SOCIETY in the office to which they were called, and then returning to the ranks to continue their efforts for the promotion of better hospital care through an enlightened program of pharmaceutical service.

Since 1946, all of these leaders have had available to them the voluntary aid of a kindly, highly efficient, exceedingly well informed and ever helpful dedicated personality who has occupied in the SOCIETY the positions of Secretary, Administrative Assistant, Associate Editor of THE BULLETIN, and Assistant Director of the Division of Hospital Pharmacy of the A.Ph.A. and ASHP.

Gloria Niemeyer Francke has never been nor aspired to be a "boss," either openly or undercover. Yet she has been the one to whom officers, committee chairmen and members generally have looked for guidance when decisions had to be made or factual information was required.

Her successful participation in the management of the affairs of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS has been so outstanding because she has adhered to the philosophy that the administrative officer or the individual chosen to perform a given task in a professional society is the *instrument* through which the society's decisions are made known and its objectives are accomplished.

As the instrument of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS for implementing its policies and objectives, she has devoted her talents and time for nearly fifteen years without stint. Like every other able administrator, she has been alert to complaints as well as praise regarding the SOCIETY'S accomplishments, but, unlike many, she has endeavored always to explore the sources of complaint and to remedy whatever might be wrong. The SOCIETY'S continuing growth is the best evidence of the reward for her untiring response to an ever-increasing demand for the services it is capable of rendering.

Today as Mrs. Francke is about to relinquish the secretaryship of the SOCIETY, she can look back with great satisfaction upon an unprecedented accumulation of substantial accomplishment which is the envy of many larger groups within the allied health professions. And we, in turn, who have had the opportunity to work with her over the years and are the beneficiaries of her devoted efforts, can bask in the reflected glory that envelops our SOCIETY as a result of the accomplishments to which she has contributed so much.

Mrs. Francke's enthusiasm for hospital pharmacy dates back to the time when she became an assistant to the chief pharmacist of the University of Michigan Hospital in 1944, after graduating from the School of Pharmacy of Purdue University and serving an apprenticeship in the pharmacy of her home town, Dillsboro, Indiana. Experience as a high school teacher and as an instructor in the School of Pharmacy of her *Alma Mater* preceded her hospital pharmacy experience, which, in turn, was followed by an invitation in 1946 to join the headquarters staff of the American Pharmaceutical Association in Washington, D. C.

Here she was first assigned to editorial duties on the Practical Pharmacy Edition of the Association's Journal, having had previous editorial experience in the production of THE BULLETIN OF THE AMERICAN SOCIETY OF HOSPITAL PHARMACISTS when the publication was still in its infancy. This connection with THE BULLETIN has been maintained right through the period when it became the AMERICAN JOURNAL OF HOSPITAL PHARMACY, of which she continues to be the associate editor.

Mrs. Francke became the mainstay of the office of the Secretary of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS at the time the SOCIETY emerged from relative obscurity to occupy an ever more important role in American pharmacy. She worked closely with the Secretary of the American Pharmaceutical Association who became the Chairman of the Policy Committee of the Division of Hospital Pharmacy when that Division was established at A.Ph.A. headquarters as the operating agency for the joint efforts of the A.Ph.A. and ASHP in promoting hospital pharmacy.

There are some things which the secretary of an organization accomplishes because it is the wish of the membership that they be carried out. There are other things which a good Secretary undertakes on his or her own initiative. Mrs. Francke had the opportunity as Secretary of the ASHP, as Assistant Director of the Division of Hospital Pharmacy, and as Associate Editor of THE JOURNAL, to ignore some tasks which others would have considered too difficult or out of the reach of the organization at the time, regardless of their acknowledge importance.

Had she not been willing to put forth the extra effort at a time when there was much other work to do, we would not have today the *Comprehensive Bibliography on Hospital Pharmacy*, first prepared in 1951 and kept up-to-date for the immeasurable benefit of the profession ever since.

Had she not been willing to put forth the extra effort month after month in aiding others, we would not have had the continuing columns on therapeutic trends, timely drugs, abstracts, and other features of hospital pharmacy literature as complete as they have been in THE JOURNAL.

Had she not been willing to extend her efforts almost to the point of exhaustion, we would not have had the *Ten Year History of the American Society of Hospital Pharmacists* which became available in 1952, nor would we have had the recognition that has come to hospital pharmacists as a well coordinated group which systematically provides for its own continuing education through hospital pharmacy institutes and other educational efforts.

Mrs. Francke—Gloria, as we who have worked with you usually address you—these are but a few of your regular and extra-curricular activities from which hospital pharmacists and the profession of pharmacy in general have benefited and will continue to benefit for years to come.

The above tribute to Gloria Niemeyer Francke, Secretary of the American Society of Hospital Pharmacists from 1949 until 1960, was presented by Dr. Robert P. Fischelis. Following presentation the final resolution was read.

We admire and appreciate the high fidelity which has characterized the discharge of your duties as the Society's administrative officer. We honor you for your unremitting devotion to the specialty which we have chosen as the medium for our contribution to the healing arts. We respect you for the integrity with which you have upheld the ethical principles to which our profession subscribes in its relations with the other health professions and the public. We love you for the interest you have shown in so many ways and so many times in our personal problems and in our personal welfare.

May the knowledge of our great appreciation of your efforts as manifested to you in these closing days of your brilliant official services and God's blessing abide with you always in your future endeavors.

13

Appreciation on Behalf of Society

WHEREAS Gloria Niemeyer Francke has served brilliantly and faithfully as Secretary of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS since 1949 and

WHEREAS the administration of her office has been a major contribution to the rapid growth of the SOCIETY, therefore be it

RESOLVED that the SOCIETY by a rising vote of thanks add its hearty approbation to Dr. Fischelis' tribute to our Gloria Francke.

Affiliated Chapters

Delegates to 1960 Annual Meeting

SOUTHEASTERN
Terry B. Nichols
Lillian Price

SOUTHERN APPALACHIAN
W. B. Rhodes

ALABAMA
Mary Lancaster

ARIZONA
Eli Schlossberg

ARKANSAS
George Provost

NORTHERN CALIFORNIA
Paul H. Honda

SAN DIEGO
No delegate

SOUTHERN CALIFORNIA
Frank Gianetti
Joseph A. Winestock

COLORADO
J. Conklin LaNier

CONNECTICUT
No delegate

FLORIDA
Weldon R. Rehburg

DADE COUNTY
Eleanor Moran

GEORGIA
Rheta Leverett

MIDWEST
No delegate

ILLINOIS
Charles Lev

INDIANA
Eileen Foley

IOWA
Warren Gaffney, Jr.

IDAHO
No delegate

LOUISIANA
William M. Hanna

MARYLAND
Mary W. Connelly

MASSACHUSETTS
Ethel Pierce

MICHIGAN
Jane Rogan

MINNESOTA
Neil Schwartau

MISSISSIPPI
Fred W. McEwen

KANSAS CITY
Moses M. Speiser

GREATER ST. LOUIS
Sister Mary Tarcissa

NEBRASKA
Lillian Dorsey

NEW JERSEY
Florence S. Frick

GREATER NEW YORK
Sister Mary Donatus

NORTHEASTERN NEW YORK
Janet D. McFadyen

ROCHESTER AREA
Norman Gallagher

SOUTHEASTERN NEW YORK
Joel Yellin

WESTERN NEW YORK
Melvin Monteith

NORTH CAROLINA
Gerald Stahl

NORTH DAKOTA
Sister M. Emmanuel

OHIO
Theodore Mink

AKRON AREA
Jeannette Sickafoose

CENTRAL OHIO
Kurt Kleinmann

GREATER CINCINNATI
No delegate

CLEVELAND
Mary Ann Yanosek

TOLEDO
Sister Mary John

OKLAHOMA
Sister M. Teresa

OREGON
No delegate

EASTERN PENNSYLVANIA
Herbert L. Flack

WESTERN PENNSYLVANIA
James Sandala

RHODE ISLAND
No delegate

SOUTH CAROLINA
Rachel Chrysostom

TENNESSEE
Mary Bowles

HOUSTON AREA
Paul D. Wilburn

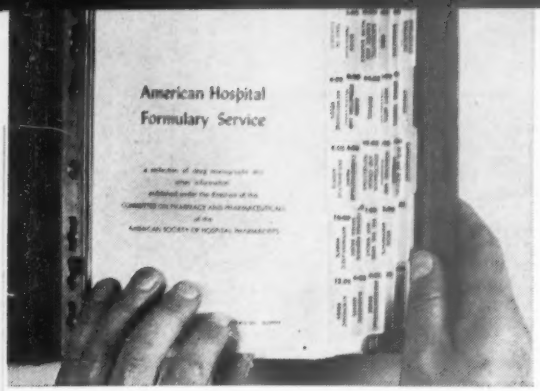
TEXAS
Guy Kelly

UTAH
Nellie Vanderlinden

VIRGINIA
No delegate

WASHINGTON STATE
Theodore Taniguchi

WISCONSIN
Elmer E. Unke



AMERICAN HOSPITAL FORMULARY SERVICE

edited by WILLIAM HELLER, *Chairman ASHP Committee on Pharmacy and Pharmaceuticals*

Seventh Supplement

► THE SEVENTH AHFS SUPPLEMENT, which was distributed in August, contained monographs on the following drugs:

furazolidone (Furoxone) (incl. Tricofuron) 8:32
furazolidone (Furoxone) 8:40
dicyclomine (Bentyl) hydrochloride (incl. Kolantyl, Bendectin) 12:08
hexocyclium methylsulfate (Tral) (incl. Tralcyon) 12:08
phenprocoumon (Liquamar) 20:12.04
hexadimethrine bromide (Polybrene) 20:12.08
sodium 2-ethylhexyl sulfate (incl. Tergimist, Tergitol 08) 48:00
*dexamethasone (Decadron, Deronil, Gammacorten) (incl. Decabamate, Decagesic, Delenar) 68:04
*methylprednisolone (Medrol) (incl. Depo-Medrol, Solu-Medrol) 68:04
triclobisonium (Triburon) chloride 84:04.16

Eighth Supplement

► THE EIGHTH AHFS SUPPLEMENT, a 32-sheet supplement, is planned for October. This supplement will mark the establishment of the following new subcategories:

8:12.04 Antifungal Antibiotics
8:12.08 The Chloramphenicols
8:12.12 The Erythromycins
8:12.16 The Penicillins
8:12.20 The Streptomycins
8:12.24 The Tetracyclines
8:12.28 Other Antibiotics
28:16.04 Antidepressants
28:16.08 Tranquilizers
28:16.12 Other Psychotherapeutic Agents

A new Table of Contents page and a change sheet will be included with this supplement. Monographs tentatively scheduled for the eighth supplement include:

The Erythromycins (general statement) 8:12.12
erythromycin (Ilotycin) 8:12.12
erythromycin (Ilotycin) ethylcarbonate 8:12.12
erythromycin (Erythrocin) ethylsuccinate 8:12.12
erythromycin (Ilotycin) glucoheptonate 8:12.12
erythromycin (Erythrocin) lactobionate 8:12.12
erythromycin propionate (Ilosone) (incl. Ilosone Sulfa) 8:12.12
erythromycin propionate (Ilosone) lauryl sulfate (incl. Ilosone Lauryl Sulfate Sulfa) 8:12.12

*Revised monograph

erythromycin (Erythrocin) stearate (incl. Erythromid) 8:12.12
The Phenothiazines (general statement) 28:16.08
Comparative Structure of Phenothiazine Derivatives (table) 28:16.08
*chlorpromazine (Thorazine) hydrochloride (incl. Thora-Dex) 28:16.08
fluphenazine hydrochloride (Permitil, Prolixin) 28:16.08
*mepazine (Pacatal) 28:16.08
methoxypromazine maleate (Tentone) 28:16.08
*perphenazine (Trilafon) 28:16.08
*prochlorperazine (Compazine) (incl. Combid, Eskatrol) 28:16.08
*promazine (Sparine) hydrochloride (incl. Prozine) 28:16.08
*thiopropazate (Dartal) hydrochloride (incl. Pro-Banthine with Dartal) 28:16.08
thioridazine hydrochloride (Mellaril) 28:16.08
trifluoperazine (Stelazine) 28:18.08
*triflupromazine (Vesprin) hydrochloride 28:16.08

Other monographs which will appear in future supplements are:

*piperazine (incl. Perin, Antepar, Pipizan) 8:08
*chloramphenicol (Chloromycetin) 8:12.08
potassium phenethicillin (Alpen, Chemipen, Darcil, Dramcillin-S, Maxipen, Ro-Cillin, Syncillin) 8:12.16
biperiden (Akineton) hydrochloride 12:08
methoxamine (Vasoxyl) hydrochloride 12:12
*chlormezanone (Trancopal) (incl. Trancoprin) 12:20
chlordiazepoxide (Librium) hydrochloride 28:16.08
benactyzine hydrochloride (Phobex, Suavitil) (incl. Deprol) 28:16.12
potassium gluconate (incl. Kaon) 40:12
spironolactone (Aldactone) 40:28
*fibrinolysin (human) (Actase, Thrombolysin) 44:00
benzonatate (Tessalon) 48:00
glyceryl guaiacolate (incl. Robitussin) 48:00
thimerosal (Merthiolate) 52:04.12
cetylpyridinium (Ceepryn) chloride (incl. Cepacol) 52:28
oxethazaine hydrochloride (incl. Oxaine) 56:04
pipamazine (Mornidine) 56:20
*triamcinolone (Aristocort, Kenacort) (incl. Aristogesic, Aristomin, Aristocort Parenteral, Kenalog Parenteral) 68:04
cetylpyridinium (Ceepryn) chloride 84:04.16
merbromin (Mercurochrome) 84:04.16
thimerosal (Merthiolate) 84:04.16

There are dozens of other AHFS monographs in some stage of preparation. Monographs on amine oxidase inhibitors for the new subcategory on Antidepressants 28:16.04 will soon be released, as well as monographs on such newer drugs as triparanol (MER 29), mepivicaine (Carbocaine) hydrochloride, para momycin (Humatin), methandrostenolone (Dianabol), and guanethidine (Ismelin) sulfate.

Consulting WITH BOWLES

GROVER C. BOWLES JR., *Baptist Memorial Hospital, Memphis, Tennessee*

► Our local group is developing a professional relations board to aid in local personnel placement and to enter into arbitration, when requested, between administrators and pharmacists when problems arise, such as firing, salary increases and other problems. What is your opinion of this type of thing?

The personnel placement portion of your professional relations program will probably fill a much needed service for hospitals and pharmacies. However, I seriously doubt if the arbitration phase of your program will serve any useful purpose to either the pharmacists or the hospital administrators and could well work to the detriment of your group.

Certainly, I would not want any outside group suggesting to my administrator that I should have a salary increase. This is a private matter between the two of us. Likewise, I doubt if many administrators would be inclined to submit their action in the firing of a department head to arbitration by an outside group.

► Should we attempt to prepare our own formulary or purchase a reputable formulary and revise it to suit the needs of our hospital?

With the excellent *American Hospital Formulary Service* available, few if any, hospitals will find it practical to prepare their own formulary. Using the A.H.F.S., your Pharmacy and Therapeutics Committee selects the monographs for those drugs they wish to include in the formulary of your hospital. These monographs are carefully prepared and provide brief, objective and unbiased information about drugs. More important, the A.H.F.S. provides a flow of monographs on new drugs and continuous revision as more information is available.

For additional information about the *American Hospital Formulary Service* and sample monographs, write to William M. Heller, Ph.D., Director, American Hospital Formulary Service, University of Arkansas Medical Center, Little Rock, Arkansas.

► What is a stock drug?

In hospital pharmacy, stock drugs are those drugs stocked at the nursing station and available for immediate use. Usually stock drugs are divided into two categories. Those for which no charge is made are usually referred to as stock drugs or non-charge floor stock drugs. Those drugs for which a charge is made are usually referred to as charge floor stock drugs.

► How do you control charge drug floor stocks? Do you receive charges for all medications or do you have a substantial loss?

Even under the best control systems, it is doubtful if you can recover a charge for every item. For this reason, inventory shrinkage should be considered when establishing a charge for these items.

These steps will minimize your losses: (1) limit floor stock charge items to single dose medications, (2) establish a definite inventory for each item. This should be determined by the head nurse and the pharmacist and may vary from floor to floor, (3) make replacements only when charges are sent to the pharmacy, (4) require nursing office approval for all requests for replacements not accompanied by charge slips.

► Does any hospital pharmacy have 24 hour coverage by pharmacists? If so, how effective has the night shift (11:00 P.M. - 7:00 A.M.) been in services rendered and in economy?

Yes, a few hospitals do provide round-the-clock pharmacy service with a pharmacist on duty at all times. Most of us will agree that this is the only way complete pharmaceutical service can be provided to the patient and the hospital staff. Likewise, we will agree that 24 hour coverage presents a number of practical problems. First, due to the shortage of pharmacists which exists throughout the country, it is difficult to find pharmacists that are willing to work the 11-7 shift. Secondly, it is expensive. Most hospitals now operate on a basic 40 hour week and people on the night shift must be relieved for days off, vacation and illness. While some duties such as bulk compounding, inventory control, packaging and other productive work can be assigned to the 11-7 shift, for the most part the work formerly accomplished in 10 to 12 hours is now diluted to 24 hours. Certainly, 24 hour pharmacy service is desirable but it is also costly. Perhaps it would be wise to extend pharmacy service from 7:00 A.M. to 11:00 P.M. before attempting to provide 24 hour coverage.

► How much does a part-time pharmacist earn in a hospital pharmacy?

Usually, a part-time pharmacist is paid the going hourly rate for relief pharmacists in the community. However, salary is a private matter to be negotiated between the employee and the employer.

News

Bowles Elected Chairman of A.Ph.A. House of Delegates

Grover C. Bowles, Chief Pharmacist at Baptist Memorial Hospital in Memphis, Tennessee, was elected Chairman of the American Pharmaceutical Association's House of Delegates at the recent Convention in Washington. Mr. Bowles served a term as president of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS and is a past president of the Memphis Retail Drug Association. He has also recently completed a term on the A.Ph.A. Council. Elected as Vice-Chairman was Dean John Adams of Duquesne University School of Pharmacy, Pittsburgh. The election for these officers took place at the final session of the House of Delegates during the Convention.

At the same time, nominations for A.Ph.A. officers and council members were made as follows:

For President—J. W. Lansdowne, Indianapolis, Indiana; Stephen Wilson, Detroit, Michigan; and Thomas D. Wyatt, Spartanburg, South Carolina.

For First Vice-President—Calvin Berger, New York, New York; R. H. Blythe, Philadelphia, Pennsylvania; and John J. Dugan, New Haven, Connecticut.

For Second Vice-President—Noel E. Foss, Baltimore, Maryland; Thomas A. Foster, Washington, D. C.; and L. F. Tibbetts, Arlington, Massachusetts.

For the Council—F. S. Ballasone, Baltimore, Maryland; H. M. Burlage, Austin, Texas; T. C. Daniels, San Francisco, California; W. J. Dixon, Oak Hill, West Virginia; Herbert H. Gerding, Fort Wayne, Indiana; Robert J. Gillespie, St. Joseph, Michigan; Howard C. Newton, Boston, Massachusetts; J. Curtis Nottingham, Williamsburg, Virginia; and George L. Scharringhausen, Jr., Park Ridge, Illinois.

Ballots for the election of A.Ph.A. Officers and council members will be mailed to all active members in good standing within the next 60 days.

► RALPH S. MURPHY, New Castle, Delaware, has been appointed Chief Pharmacist to Pennsylvania Hospital's Department for Sick and Injured in Philadelphia. The announcement was made by Mr. H. Robert Cathcart, Vice President of the Hospital.

A native of Camden, New Jersey, Mr. Murphy attended Rutgers University. Following graduation from the Philadelphia College of Pharmacy and Science in 1954, he studied under a one-year pharmacy residency at Jefferson Medical College Hospital, Philadelphia. From 1955 to 1958, Mr. Murphy served in the United States Air Force. Upon his return to civilian life, he was employed as a retail pharmacist.

In his new post, Mr. Murphy succeeds Mrs. Vera Durando, who died June 18. Mrs. Durando had been at Pennsylvania Hospital since 1938, and had held the post of chief pharmacist since 1948.

► HOSPITAL PHARMACIST NORBERT R. WEGEMER, of the Little Traverse Hospital in Petoskey, Mich., is the 1960 recipient of the A. H. Robins "Bowl of Hygeia" award for outstanding community service. Wegemer received the award June 8 at the annual convention of the Michigan State Pharmaceutical Association (MSPA) in Detroit.

The recipient, an honorary life member of the MSPA, also belongs to the Northern Michigan Pharmaceutical Association, AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, Michigan Academy of Pharmacy, and the Federation Internationale Pharmaceutique.

The Award plaque, presented annually through the state pharmaceutical association, is modeled after a sterling silver bowl made by a Mexican silversmith and presented to the A. H. Robins Co. by its Latin-American representatives on the Richmond, Va., ethical pharmaceutical manufacturing firm's 75th anniversary in 1953.

Index Chemicus Launched

Index Chemicus, a monthly index to more than 60,000 new chemicals reported each year in the scientific literature, has been introduced by the Institute for Scientific Information, Philadelphia, Pa.

The inaugural issue reports over 3700 newly synthesized compounds. It is being warmly received by leading chemists who are hailing *Index Chemicus* as a "significant breakthrough" in chemical documentation.

In the preparation of the *Index Chemicus* new techniques in information handling are employed. These techniques utilize both manual and machine methods for handling chemical information. The *Index Chemicus* is checked for accuracy on a computer which then prints out the molecular formulas.

Index Chemicus contains listings of chemical names, structural diagrams, and molecular formulas as well as complete bibliographical information including ar-

ticle title, authors, institutions, addresses, and original journal references and page locations for each compound. In addition, indexes are cumulated quarterly and yearly.

The techniques used in compiling the *Index Chemicus* were developed by the Institute for Scientific Information as a by-product of a steroid coding project performed for the Pharmaceutical Manufacturers' Association and the U. S. Patent Office for the past three years.

For further information, contact the Institute for Scientific Information, 1122 Spring Garden Street, Philadelphia 23, Pa.

► CHARLES M. KING, JR., has recently accepted the position as Director, Department of Pharmacy, Barberton Citizens Hospital in Barberton, Ohio. Mr. King was formerly with the U. S. Public Health Service Indian Hospital in Shawnee, Oklahoma. He holds a Masters Degree from the Philadelphia College of Pharmacy and Science and served an internship at the Jefferson Medical College Hospital in Philadelphia. Mr. King is currently serving as Chairman of the SOCIETY's Committee on Classification and Filing Systems for Hospital Pharmacy.

Abbott's Survey of Brand Name Prescribing

Brand name drugs prescribed most often by American physicians are made by 56 different manufacturers, reports David D. Stiles, Director of Market Development at Abbott Laboratories.

"Far from being monopolistic, as charged in the Kefauver hearings, the drug industry offers unusual opportunities for many firms, large and small, to share in the market," he says.

"Of the 409 most prescribed drugs listed by the Continuous Prescription Survey, 341 were brand name specialties, while 68 were generic name competitive drugs," Stiles reports. "Together they accounted for 78 per cent of the prescription market in 1959."

Stiles points out that the 68 leading generic name drugs represented about 75,000,000 prescriptions. These were filled with the products of perhaps several hundred manufacturers. "Contrary to impressions given in the Kefauver hearings, this reveals that pharmacists can fill many prescriptions, if they wish, with generic name products," the Abbott executive emphasizes.

Stiles points out that 1,300 firms share in the manufacturing and distribution of drugs in America and that of the 140 members of the Pharmaceutical Manufacturers Association, 60 percent have a sales volume of less than $5,000,000 annually.

The Survey shows that the number of products prescribed with the greatest frequency (five or more times per 10,000 prescriptions) has stayed at about 400 for some years. This happens regardless of the hundreds of new products introduced annually. In 1959, 66 products from 32 manufacturers dropped out of the top 400, while 67 products, coincidentally also from 32 manufacturers, climbed to the 400 listing.

THE TENTH ANNUAL INSTRUMENT SYMPOSIUM and Research Equipment Exhibit will be held at the National Institutes of Health, Bethesda, Maryland, October 4-7, 1960. The Symposium will include recent developments in research methods and instrumentation with the primary topics for discussion as follows: fluorescence; infra-red; activation analysis; ultracentrifuge; microscopy; and electrodes. The exhibit will include the latest types of research equipment by instrument manufacturers.

1960 AAAS Meeting

A request for titles of papers to be presented at the Pharmacy Section meeting of the American Association for the Advancement of Science has been made by Dr. John E. Christian, Secretary, Section Np, Purdue University, School of Pharmacy, Lafayette, Indiana. Meetings are to be held in New York City the week starting December 26.

The Pharmacy Section meeting will start Tuesday, December 27, at 9:00 A.M. with Contributed Paper Sessions in Hospital Pharmacy and will be followed by Contributed Paper Sessions from other areas of scientific pharmacy on December 29 and 30.

Authors who wish to present papers before the contributed paper sessions to be held on Thursday and Friday, December 29 and 30, are requested to send in titles of papers along with an original and one copy of a short abstract *as soon as possible*. All titles and abstracts for inclusion in the printed program must be in by *September 20*.

Submitted papers in general should require not more than 15 minutes for presentation. A copy of the completed manuscript is required not later than the time of the meeting and authors may publish in the journal of their choice.

The center of the meeting will be Biltmore, Commodore and Roosevelt Hotels which will accommodate the general sessions of the AAAS, the Annual Exposition of Science and Industry, and the AAAS Main Registration Information Center. The Pharmacy Section headquarters and meetings will be in the Roosevelt Hotel.

ABSTRACTS OF PAPERS

presented at the 19th International Congress of Pharmaceutical Sciences of the International Pharmaceutical Federation Zurich, Switzerland, September, 1959

A series of abstracts presented at the 19th International Congress of Pharmaceutical Sciences of the International Pharmaceutical Federation is appearing in THE JOURNAL. The first of the series were those presented in English and appeared in the January issue. In the second series appearing in March, the English abstracts were continued and the beginning of those translated from the German were included. A third series concluding the German abstracts appeared in the May issue. The fourth series, which includes abstracts translated from the French, was started in the August issue and is concluded here.

ANTIBRUCELLIC PRINCIPLES

The Testing of Antibrucellic Active Principles of Hieracium Pilosella L., before and after Stabilization, (Le contrôle des principes actifs antibrucelliques de l'Hieracium pilosella L., avant et après stabilisation) by M. Haag-Berrurier and P. Duquénois, Faculté de Pharmacie, Strasbourg, France.

In various publications Duquénois and Greib have demonstrated the efficacy of preparations of *Piloselle* in brucelloses, infectious diseases common to man and to various animal species. Having studied the chemical composition of the non-stabilized plant, used for clinical and veterinary experiments, they established that the most active principle is ombelliferone; it is accompanied by substances detected on the chromatogram by their fluorescence which is different from that of ombelliferone. These are caffeic acid and chlorogenic acid, which have a slight antibrucellic action, flavonoids with a distinct effect on diuresis and certain unknown substances.

Since then, M. Haag has succeeded in determining one of the substances which previously could not be identified. It is a heteroside of ombelliferone, scarcely soluble in organic solvents, hydrolyzable by acids or emulsin; it exists in dried leaves, especially when they have been carefully stabilized. Since the antibrucellic action of this heteroside was not the same as that of the free ombelliferone, it was useful to test, other than biologically (inhibition of the growth of *Brucella abortus bovis*, cultured in bouillon) the amount of free and prepared ombelliferone in *Piloselle* leaves.

We measured the established ombelliferone by measuring the intensity of its fluorescence, with a fluorescimeter Photovolt 540, under controlled conditions. The pulverized organs dried under the same conditions, either directly or after stabilization in ethanol vapors immediately after picking, are boiled in absolute ethanol and the alcoholic liquids are chromatographed on alumina. The eluate, which contains neither flavonoid pigments, caffeic acid or its derivatives, nor prepared ombelliferone, is evaporated and the residue recovered by a solution of phosphates which precipitates the chlorophyl, but completely dissolves the free ombelliferone which was measured with the fluorescimeter. The same amounts are recovered after hydrolysis of *Piloselle* and give total ombelliferone.

DIGITALIS CHROMATOGRAPHS

Selection Experiment with Digitalis lanata Ehrh., (Essai de sélection chez Digitalis lanata Ehrh.) by L. Fauconnet, Ecole de Pharmacie, Université, Lausanne, Suisse.

We have perfected a technique of chromatographic analysis on paper, capable of giving a great series of qualitative and quantitative results (12 cardenolides detected and determined) with individual specimens from 0.1 to 0.5 Gm. of dried leaf., The plants, from which we take two to four leaves for each analysis, continue to live and can bear fruit. We can thus examine the portions of plants individually analyzed in numbers sufficient for selection and statistical analysis of successive generations. At the beginning of our work (1952-1953) we had 125 plants, of which 64 have borne fruit after self-fertilization. Following selection by several criteria, we maintained 14 descendants of self-fertilized biennial plants of which we analyzed the leaves once or several times during the year, for four successive generations.

From one generation to another each descendant becomes more homogeneous in its morphological characteristics, but also in the amounts of cardenolide heterosides. The related side-types of each family of 25 sister plants diminish from one generation to the other. Simultaneously the differences between the various descendants become more pronounced: the dispersion of the average values of the descendants increases from one generation to another. These two general results indicate that a selection such as we used is effective.

DETERMINATION OF MUSTARD OIL GLUCOSIDES

A Colorimetric Method for the Determination of Mustard Oil Glucosides, (Une méthode colorimétrique pour le dosage des glucosides sénévoliques) by L. Carreras Matas, Instituto José Celestino Mutis de Farmacognosia, Madrid, Spain.

A method for the determination of very small quantities of mustard oil glucosides is described. The method is as follows:

The mustard oil glucosides are decomposed with 6N sulfuric acid; the hydroxylamine produced is converted into nitrous acid which reacts with sulfanilic acid and the diazo compound formed couples with alpha-naphtylamine. The original quantity of glucoside is deduced from the intensity of color produced.

SOIL EROSION AND HYSSOPS

Contribution to the Study of the Possibility of Hyssop Cultivation and of Production of Essential Oil on a Large Scale, (Contribution a l'étude de la possibilité de culture d'hysope et de production d'huile essentielle à grande échelle) by Y. Tucakov, Institut de Pharmacognosie de la Faculté de Pharmacie, Université, Belgrade, Yugoslavia.

In Yugoslavia, as well as in many other countries, erosion in mountainous areas is increasing considerably, both in the area affected and the degree of severity. The heat of the sun, the warm south winds, the long dry periods, the irregularity and violence of the rains, the crumbly texture of the soil, the steep grades in many

regions of the mountains combine to produce this erosion which is so pronounced, catastrophic and in some cases tragic.

With the intention of conserving soil menaced by erosion, we have tried to cultivate a certain number of aromatic plants. In the regions of continental and steppe-like climate and in shifting sand, hyssop has given us the best results. Even in less productive soils the yield in flower heads and essential oil was favorable. The organoleptic properties and the physical-chemical constants of the oil produced generally correspond to the requirements stated in current literature. Essential oil with the terpenes removed is much more suitable. The exogenic factors of the yield and the quality of the essential oil have been studied. The general economic interest for the large-scale industrial production of hyssop oil has also been discussed.

GROWTH OF SPHACELIA SEGETUM LEVEILLE

Some Experiments on the Growth of Sphacelia segetum Leveille in Liquid Culture Mediums, Containing Casein as Nitrogen Source, (Quelques essais sur la croissance de la Sphacelia segetum Leveille dans des milieux de culture liquide, contenant de la caseïne comme source azoté) by C. González Gòmez and Filomena Díaz Celayeta, Instituto José Celestino Mutis de Farmacognosia, Madrid, Spain.

According to these experiments, casein appears to be a good nitrogen source for the growth of *Sphacelia*; in comparison with ammonium nitrate casein gave a better result in the various quantities tested. Compared to asparagine and according to the amounts added in these experiments, as well as the time of permanence in the drying-room, casein showed itself to be a source of nitrogen equal to or less than asparagine.

MAYER'S REAGENT

New Applications of Mayer's Reagent, (Applications nouvelles du réactif de Mayer) by P. Mauer, Laboratoires Kela, Hoogstraten, Belgique.

The study of alkaloids and other nitrogen bases (for example, antihistamines) makes considerable use of precipitant reagents and certain of them have been retained by the majority of the pharmacopeias.

The reagent of Mayer-Valser is one of the principal ones, but in the conditions where it is used it is totally lacking in specificity. The author proposes the modification of its use in the pharmacopeias which have retained it. This modification would give it a specificity at present unknown. A list of examples forms part of the communication.

FORMATION OF FOAMS

The Formation and Stability of Foams and Their Measurment, (La formation et la stabilité des mousses et leur mesure) by R. Ruyssen and A. Lauwers, Institut de Pharmacie de l'Université, Gand, Belgique.

The physical properties of film, constituted by the adsorption of the dissolved surfactant in the liquid phase, condition the formation and the stability of gas dispersions in liquids.

The physical state of this film functions as the structure of the foaming agent, but it can be well modified by some impurities, pH and the composition of the liquid phase.

Several different factors are to be considered; the tensio-activity and the elasticity of the film, the viscosity of the surface and that of the interior, the electrostatic action on the double electric layers formed by the two sides of the lamellae.

The duration and persistence of foams depends furthermore on the tension in the interlamellar liquid, the diameter of the bubbles, the isodisperity, and the rate of gas dispersions.

The measure of aphrogene power is very useful when the exact chemical structure of the natural foaming products (saponins, phosphatides, polypeptides) is not known, but the method must satisfy reproductibility norms. It must be dynamic and take into account the composition of the solution, the gas pressure and discharge the diameter of the capillary of escaping, gas, the temperature, the nature of the gas, and the form and dimensions of the recipient of the measurement. In measuring the tension, distinction must be made between the drainage rate of interlamellar liquid and real stability.

The described mode of operation permits measurement of the total volume of foam formed, with regard to the concentration of the foaming agent, the volume of the interlamellar liquid and the hydrostatic pressure exerted by the foam column on the generating liquid. The precision of measurement is particularly sensitive to variations of gas discharge.

The foaming power which has been determined for sapoalbine (Saponinum purum album Merck), sodium lauryl sulfate, cetyltrimethylammonium bromide (Cetavlon) is defined by the minimum concentration obtained through extrapolation and is able to furnish a persistent foam in the specified generating condition.

The "holding" of the foam is followed by the drainage rate of the liquid phase and calculated according to the Clark and Ross relation. The measurements are made immediately after stopping of the gas current for a 5 minute period. Application of the system described has shown that after a longer time, constant S undergoes a rapid increase in value.

TETRACYCLINES

New Soluble Derivatives of Tetracycline, (Nouveaux dérivés solubles de la tétracycline) by B. Gradnik, A. Pedrazzoli and E. Ferrero, Farmaceutici Midy, Milan, Italie.

To avoid the inconvenience of the parenteral administration of tetracycline, we have prepared some new soluble derivatives of this antibiotic.

Of all the synthesized elements, 9-(4-[b-hydroxyethyl]-diethylene-diaminomethyl)-tetracycline seems, particularly interesting.

The new compound is extremely soluble ($>$1.5 Gm./ml.) and its qualitative antibiotic activity is identical to that of tetracycline.

The local tolerance of the derivative is excellent; its acute toxicity when taken intravenously, taking into account molecular affinities, is the same as that of tetracycline.

The hematic antibiotic levels, one hour after intramuscular administration of 300 mg., are 20 times higher than the levels which are obtained with tetracycline chlorhydrate.

From this new compound we have prepared phosphate, citrate, glutamate and phenoxymethylpenicillate; the latter, presents some interesting antibiotic properties "in vivo" and "in vitro."

DETERMINATION OF MOISTURE

A New Method of Determining the Water in Chemical and Galenic Substances, (Une nouvelle méthode du dosage de l'eau dans les produits chimiques et les produits galéniques) by P. Boymond and M. Akdémir, Pharmacie de l'Hôpital Cantonal, Genève, Suisse.

This determination is based on the augmentation of the humidity of the air contained in a closed balloon, of known volume, when a given quantity of the substance is heated therein to evaporate the water it contains. The reading is made, with a temperature determined by the air, on a hygrometer. By abstracting the result of an experiment made white hot at the same temperature, the quantity of water contained in the intake is obtained.

We can thus measure 0.1 to 0.3 Gm. of water united to or incorporated in a substance as easily as the melting point of an element is taken. The margin of error depends on the quality of the hygrometer. Volatile organic solvents do not seem to hinder the operation.

GORLIC ACID

Extraction of Gorlic Acid from the Oils of African Flacourtiacées, (Extraction de l'acide gorlique des huiles de Flacourtiacées africaines) by Marie-Thérèse François and J. Pelt, Laboratoire de Matière médicale, Université, Nancy, France.

The antileprous activity of the oils of Flacourtiacées, still called "Chaulmoogra oil" is generally attributed to the cyclopentenic fatty acids which they contain. Among these, gorlic acid, homologue of chaulmoogric acid which differs from the former only by a double supplementary liaison in the lateral chain, seems to possess a particularly high leprostatic activity, which would be in relation with its unsaturation degree. But gorlic acid is only found in

very small proportion (10 to 15%) in the present chaulmoogra oils, in such a way that its extraction - a long and difficult process - did not produce quantities sufficient for a thorough pharmacodynamic experimentation. We have therefore been seeking for a method of rapidly furnishing significant quantities of gorlic acid. The classic methods were systematically explored without great success (distillation of ethylic esters, fractional crystallization of fatty acids, utilization of selective solvents, use of methods based on the solubility of metallic salts, etc). However, thanks to the formation of compounds with urea, it was possible to obtain appreciable quantities of gorlic acid in a state of suitable purity permitting a pharmacologic study. As a matter of fact, the monoethylenic cyclopentenic acids (chaulmoogric acid and hydnocarpic acid) unite with urea to give compounds, little soluble in methanol, but easy to separate by filtration. Gorlic acid, on the other hand, remains in solution and may be recovered by distillation of the miscella. In a primary operation about 75% of fatty acids composed solely of chaulmoogric acids, palmitic hydnocarpics, etc. can thus be eliminated, while the totality of gorlic acid centers in the 25% of fatty acids remaining in solution in the methanol. *This last fraction is purified* by applying the same treatment; thus "technically pure" gorlic acid is easily produced. The method with a 10% approximation lends itself to a rapid measuring of the gorlic acid contained in a "chaulmoogra oil."

DETERMINATION OF CHLORAMPHENICOL

The Determination of Chloramphenicol in Various Medicinal Forms, (Dosage du chloramphénicol dans diverses formes médicamenteuses), by M. Andrey and A. Mirimanoff, Laboratoire de Pharmacie Galénique, Université, Genève, Suisse

The Swiss Pharmacopoeia (Supplement II) has chosen the argentometric method for titrating chloramphenicol as a substance. The purpose of the present publication consists in trying to apply this method to the most common medicinal forms: capsules, suppositories, ointments.

1. *Capsules*: an original work intended for a future article of the Swiss Pharmacopoeia has enabled us to use the argentometric method successfully. This method presents no particular difficulty and has an advantage over the methods used by most of the other pharmacopeias (spectrophotometry, colorimetry, biological analysis), because of its great precision ($\pm$ 6%). One precaution is to extract with absolute alcohol, thus avoiding the possibility of ionized chlorine which would falsify the results.

2. *Suppositories*: The most common pharmacopeias provide no determination of the active principle. We have tried to apply the argentometric method to this form; there is no literature on this subject. The essential difficulties consist in quantitatively extracting the active principle from the various fatty excipients used in practice (the hydrosoluble excipients generally considered as unfavorable have not been experimented with in this work). The principle of extraction consists in using benzine in which chloramphenicol is insoluble and which renders soluble all the fatty excipients. Precision of the method is $\pm$ 6%.

3. *Ointments*: The amount of chloramphenicol in commercial products varies between 0.1% and 5.0%. Because the argentometric method requires about 1 Gm. of active principle, we consider it too costly to be used with ointments.

Contrary to the two preceding cases, we recommend using the spectrophotometric method, which is described with precision in several publications.

QUANTITATIVE CHROMATOGRAPHY

Comparative Study of Planimetric and Densitometric Methods in Quantitative Chromatography on Paper. Application to the Measuring of Alkaloids and Amines of Broom Genista (Sarothamnus scorparius L.) (Etude comparée des méthodes plani métrique et densitométrique en chromatographie quantitative sur papier. Application au dosage des alcaloïdes et des amines du genêt à balais (Sarothamnus scoparius L.)) by F. Jaminet, Institut de Pharmacie, Université, Liège, Belgique.

After chromatographic separation on paper, the planimetric and densitometric methods permit the measuring of the principal nitrogen azote compounds of broom genista with great precision.

The author specifies the operative conditions and compares the results obtained on the one hand by direct densitometry of separated stains and on the other hand by the measure of the surfaces of these latter by means of an improved technique which consists in using these measurements not directly on the revealed stains of the chromatogram but on a photocopy of the latter obtained by contact.

Different examples of the application of these methods are reviewed, among which:

a) extraction of spartein and oxytyramine of broom genista. Comparative yield of different extraction processes;

b) graduation of spartein and oxytyramine in stabilized alcoholatures of genista;

c) fluctuations of the amounts of spartein and oxytyramine in green branches of genista in the course of a complete vegetative cycle. Discussion and comparison with the previous results.

d) Fluctuations of the amounts of amines in the flowers and pods of genista. Considerations on the biogenesis of these amines.

e) Fluctuations of the amounts of alkaloids in the seeds of genista in the course of their formation and maturation.

DETERMINATION OF GITOXIN

The Determination of Gitoxin, (Le dosage de la gitoxine) by J. Lemli, Laboratoire de Pharmacognosie, Université, Louvain, Belgique.

The reaction of *Tattje* for the determination of gitoxin in the presence of digitoxin has been modified.

The determination of small percentages (5-15%) is not possible with the proposed reagent, the influence of digitoxin becoming too great.

By applying the reaction to extracts of digitalis leaves a supplementary coloration forms due to the action of the warm sulfuric acid on the organic impurities.

In order to eliminate these errors, sometimes very great, the following reagent is proposed:

Sulfuric Acid	50 ml.
Phosphoric Acid	50 ml.
2.5 ml of an aqueous solution of 10% Ferric Sulfate	

The reaction becomes accustomed to cold and the maximum is attained after 90 minutes. The reaction is studied in detail.

The interference of coloration due to digitoxin and to impurities is eliminated by the use of a blank. The blank is obtainable by the addition of methanol which causes only the coloration of the gitoxigenin to disappear.

It was observed that the gitoxigenin and digitoxigenin obtained by hydrolysis (in the medium HCl 0.4 n) are not stable in the presence of air. It is necessary to measure the gitoxigenin obtained by hydrolysis immediately after evaporation of the organic solvent.

CURRENT LITERATURE

. . . also calling your attention to the following articles appearing in recent hospital and pharmaceutical journals

. . . . . .

ADMINISTRATION

—Cost of Drugs

Narinian, George: Pharmaceutical Pricing in Hospitals, *Hosp. Management* 90:83 (Aug.) 1960.

PARENTERAL SOLUTIONS

Smith, B. H.: The Preparation of Parenteral Injections in Ampoules: 1, *Public Pharm.* (Great Britain) 17:163 (June) 1960.

SMALL HOSPITALS

Schmid, Fred W. and Kahn, Sidney: Pharmacist-Purchasing Agent, *Hospitals* 34:60 (July) 1960.

GENERAL

Sutaria, R. H. and Williams, F. H.: Some Pharmaceutical Observations on a New Use for Urea—Part 1, *Public Pharm.* (Great Britain) 17:168 (June) 1960.

DRUG EVALUATIONS

by the Council on Drugs of the American Medical Association

► THE FOLLOWING MONOGRAPHS and supplemental statements on drugs have been authorized by the Council on Drugs of the American Medical Association for publication and inclusion in *New and Nonofficial Drugs*. They are based upon the evaluation of available scientific data and reports of investigations.

The issue of the *Journal of the American Medical Association* from which each monograph has been taken is noted under each monograph. Monographs in this issue of the JOURNAL include those published in the *A.M.A. Journal* for June 4* and June 11.

Notice

New and Nonofficial Drugs 1960 is now available from your local bookstore and from the publishers, J. B. Lippincott Company, Philadelphia, Pa. This 1960 edition contains monographs of drugs evaluated by the Council on Drugs of the American Medical Association and published in the Journal of the A.M.A. to October 17, 1959. The indexes listed below contain those drugs evaluated and published between October 24, 1959 and June 11*, 1960.

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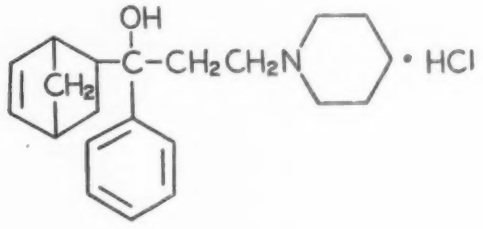
NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. KAUTZ, M.D., *Secretary.*

Biperiden Hydrochloride — Akineton Hydrochloride®

BIPERIDEN HYDROCHLORIDE (Akineton Hydrochloride) is α-(bicyclo[2.2.1]hept-5-en-2-yl)-α-phenyl-1-piperidinepropanol hydrochloride.—The structural formula of biperiden hydrochloride may be represented as follows:



Actions and Uses

Biperiden hydrochloride, like trihexyphenidyl, procyclidine, and cycrimine hydrochloride, to which it is chemically related, is an anticholinergic agent employed in the symptomatic management of paralysis agitans (parkinson's disease). The available evidence suggests that it closely resembles the older drugs in this group in range of usefulness, effectiveness, and side-effects. Thus, in patients responding favorably, it appears to effect a reduction in rigidity, to suppress excessive salivation and sweating, to improve gait and the ability for self-care, and to reduce the incidence and severity of oculogyric crises. There is little effect on tremor and only questionable improvement in the patient's mental outlook. It must be pointed out, moreover, that biperiden hydrochloride has not been adequately studied in the clinic and that the effects described are largely clinical impressions not yet confirmed by carefully planned experimentation. There is no evidence that the drug is superior to other antiparkinsonian agents. It seems to be less effective in the arteriosclerotic form of the disease than in the postencephalitic or idiopathic forms or in drug-induced parkinsonism-like syndromes. There is as yet no known contraindication to its use in conjunction with other antiparkinsonian drugs.

Biperiden hydrochloride also has had limited trial in the management of the spasticity associated with hemiplegia, injuries of the spinal cord, cerebral palsy, multiple sclerosis, and other disorders involving the pyramidal tract. The data supporting its usefulness in these conditions are, at best, only suggestive. Few patients seem to experience more than minimal improvement from its use; in spastic hemiplegia, many patients given this therapy become weaker, with consequent impairment in the ability to move or walk. Purported beneficial effects include diminution of muscular spasm and facilitation of physiotherapy in patients with cerebral palsy and suppression of hyperhidrosis in patients with paraplegia due to spinal cord injuries.

Pharmacological studies indicate that biperiden hydrochloride has the spasmolytic and antisecretory actions typical of anticholinergic agents. It is one twenty-fifth as active as atropine in antagonizing the spasmogenic effects of cholinergic agents on the intestine, about one-third as active as atropine in inhibiting salivation, and about one-sixth as potent as a mydriatic agent. The drug antagonizes the effects of nicotine on the blood pressure and nictitating membrane and prevents nicotine convulsions.

Side-effects include dryness of the mouth, blurred vision, dizziness, and gastric irritation. Minor side reactions can be minimized by proper adjustment of dosage and often become less troublesome with continued use of the drug. The drug seems to be comparatively free from untoward psychic effects, but restlessness and mental confusion occasionally occur; transient psychotic reactions have also been reported. Urinary retention and hematuria (each reported in a single case) have followed the administration of the drug to children. Like other atropine-like agents, biperiden hydrochloride should be used with great caution, if at all, in the presence of glaucoma or prostatic hypertrophy.

Dosage

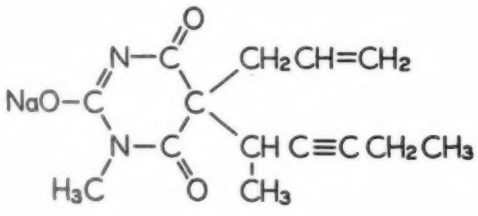
Biperiden hydrochloride is administered orally. The dose must be adjusted in accordance with the needs and tolerance of each patient; 2 mg. three or four times daily is suggested as an average requirement. Untoward effects are sometimes avoided by giving very small doses initially and gradually increasing the dose as needed. Gastric irritation is less troublesome if the drug is given during or after meals.

Preparations

Tablets 2 mg.
Year of introduction: 1959.
Knoll Pharmaceutical Company cooperated by furnishing scientific data to aid in the evaluation of biperiden hydrochloride.
J.Am.Med.Assoc. 173:675 (June 11) 1960.

Methohexital Sodium — Brevital Sodium

METHOHEXITAL SODIUM (Brevital Sodium) is sodium *α-dl*-1-methyl-5-allyl-5-(1-methyl-2-pentynyl)barbiturate. — The structural formula of methohexital sodium may be represented as follows:



Actions and Uses

Methohexital sodium, an ultrashort-acting barbiturate, is used intravenously as a general anesthetic agent. It is similar in action to thiopental sodium and related ultrashort-acting barbituric acid derivatives. However, it differs from thiopental in a number of respects. Methohexital is more potent than thiopental and consequently produces the same degree of anesthesia with smaller doses. However, much of the initial dose of thiopental apparently is absorbed by the fatty tissues and is later released back into the circulation, which permits smaller maintenance dosage near the end of anesthesia. On the other hand, methohexital, which is not absorbed by fatty tissue to the same degree, requires constant dosage to maintain an even level of anesthesia. Thus, the total dose of methohexital approaches that of thiopental after a period of three hours of anesthesia. Induction of anesthesia with methohexital is as rapid as it is with thiopental, but recovery from anesthesia is more rapid with methohexital than with thiopental.

Methohexital sodium may be used for the induction of general anesthesia or as the sole anesthetic agent for minor operative procedures which do not require muscle relaxation. It can be given by intermittent or by continuous drip techniques. When administered intermittently, more frequent injection is necessary with methohexital than it is with the thiobarbiturates. This is true especially when the drug is used as the sole anesthetic agent because of the rapid metabolism of this agent. For operations requiring muscle relaxation, methohexital must be supplemented by a gas anesthetic such as nitrous oxide plus oxygen. When methohexital is administered along with a gas anesthetic and a muscle relaxant, the resultant anesthesia is smoother and can be maintained with smaller doses of each agent. On the basis of data thus far available, it would appear that the principal advantage of methohexital lies in the patient's relatively short recovery period following cessation of its administration. The blood concentration of methohexital in experimental animals three hours after cessation of anesthesia is approximately 40% of the concentration in the blood at the end of the third hour of anesthesia; under the same conditions, the blood level of thiopental is 80%.

Side Effects

Methohexital sodium administration may be associated with muscle twitching or more severe convulsive movements due to motor excitation, sneezing, coughing, hiccuping, laryngospasm, and respiratory stridor. These may appear when induction of anesthesia is too rapid or, conversely, when the induction dose is inadequate and/or given too slowly for the patient to reach the proper depth of anesthesia. Respiratory depression and/or apnea, dangers inherent in the use of any barbiturate given intravenously, may occur. Therefore, alertness is essential to avoid the effects of overdosage. Postanesthetic shivering, associated with a marked fall in body temperature, has been observed in a few cases. Administration of this agent should be performed only by individuals well versed in the use of anesthetics given intravenously; facilities for providing oxygen and for insuring a patent airway and adequate respiration should be available at all times. As with other intravenously administered barbiturates, methohexital should be used cautiously in patients with respiratory obstruction, asthma, severe hypotension or hypertension, myocardial disease, congestive heart failure, anemia, and extreme obesity. Although the avenues of detoxication and excretion of methohexital have not yet been elucidated, the drug is probably contraindicated, as are other barbiturates, in patients with severe hepatic dysfunction.

Methohexital may be used with any of the usual preanesthetic medicaments. Although it does not cause muscle relaxation, the drug is compatible with any of the skeletal muscle relaxants and may be given concomitantly.

Dosage

Methohexital sodium is administered only by the intravenous route. The techniques, procedures, and precautions for its administration are the same as with other ultrashort-acting barbiturates used as general anesthetics.

For the induction of anesthesia, 70 to 100 mg. (7 to 10 cc. of a 1% solution) will usually suffice. For intermittent administration in the maintenance of general anesthesia (as supplemented by a gaseous anesthetic plus oxygen), small doses ranging from 20 to 40 mg. (2 to 4 cc. of a 1% solution) may be injected at intervals governed by the usual signs relating to the depth of anesthesia. A 1% solution also may be used for administration by continuous intravenous drip.

Preparations

Powder (injection) 500 mg. and 2.5 Gm.
Year of introduction: 1960.
Eli Lilly and Company cooperated by furnishing scientific data to aid in the evaluation of methohexital sodium.
J.Am.Med.Assoc. 173:676 (June 11) 1960.

Initial Treatment Of Burns

BEN J. WILSON, M.D. *and* JERRY A. STIRMAN, M.D., *Dallas, Texas*

► THE INITIAL TREATMENT OF BURNS must be directed against the effects of injury that are likely to kill the patient immediately. However, since some of the lethal derangements are only transient, the treatment used for these conditions may remain as an additional load after the initial derangements of the injury are corrected. Thus, the patient must recover from the late effects of injury as well as the residual effects of earlier treatment. Overtreatment has been responsible for many deaths of salvable persons with burns. Putting into practice a philosophy of management based on these concepts, one is obliged to use treatment measures which are not only immediately effective but also from which rapid recovery or physiological adjustments can be made.

Treatment of Shock

Since it is well established that a severely burned person will soon die in shock as a result of deficient circulating fluids and blood, the treatment of this state should consist of volume replacement with a substance which will not induce an illness incident to its effect of overcoming peripheral vascular collapse. Although the most effective volume expander is whole blood, this substance does not satisfy the criteria of an ideal repair solution because it diffuses slowly out of the vascular tree and is rather slowly metabolized and excreted. Even though these properties of whole blood are classically regarded as being advantageous, the whole blood which is given in the first 48 hours after thermal injury may remain to retard recovery in the next phase of convalescence from burns. In support of the thesis that transfusions of whole blood may exert a detrimental effect on recovery, a comparison is made of the mortality of similarly burned persons who were treated in the first 48 hours (with or without whole blood) at the Parkland Memorial Hospital, Dallas, Texas. Both groups received a balanced salt solution by vein or mouth, regardless of whether whole blood was given. No person in the blood-saline series received more than 1,000 cc. of blood in a 24-hour period, and most of the adults received 500 cc.; the children were given proportionately less. The volume of blood recommended by Evans' formula was seldom given. The mean volume of total fluid administered in the first 48 hours did not differ between the blood-saline group and the saline solution only group.

Clinical Material.—The subjects of this study were drawn from 430 burned persons seen in the hospital from 1952 to 1956. All patients who received treatment in another hospital before being sent to Parkland or who were transferred from Parkland prior to completion of treatment were excluded from the study. First degree burns were not counted in the estimate of total area of burn. Patients with burns that involved less than 15% of the body's surface were not included in the analysis of results because they did not need early replacement therapy. All other persons under 61 years of age whose burns covered less than 65% of the body's surface were included. The mortality expectancy, as defined by Bull and Squire's[1] probit analysis, in the age-excluded group approaches 100% with burns that involve only one-fifth of the body's surface. In the area-excluded group, the mortality expectancy is nearly 100%; therefore, these patients were removed from the series because the effects of a variable in treatment cannot be assessed in uniformly fatal injuries when only survival is used as the criterion of treatment success.

Any postburn death, regardless of cause, that occurred in the hospital was included, even though the burn may have been healed prior to death. In all probit analyses and in comparisons of series from different hospitals or from different time periods, all deaths are included. The only exception is the exclusion of tracheobronchial burns when comparisons are made of results between two therapeutic groups which were treated during the same period in the same institution; in this kind of comparison, the patients with tracheobronchial burns are excluded because this is a uniformly fatal injury. The tables in this report have been labeled to indicate whether tracheobronchial burns are excluded.

TABLE 1.—*Parkland 1952-1956 Series Showing Mortality According to Burn Area and Treatment**

Burn Area, % Body Surface	Mortality, %				Patients, No.	
	First 10 Days		Total			
	Blood-Saline	Saline Only	Blood-Saline	Saline Only	Blood-Saline	Saline Only
15-24	0	0	0	1.5	4	65
25-44	8	0	25	2.5	12	39
45-64	67	0	89	30.0	9	13
Total					25	117

* Tracheobronchial burns excluded; patients less than 61 years of age.

Results of Shock Treatment: In table 1, the mortality for the blood-saline and saline solution only groups is divided into the deaths that occurred within 10 days of injury and the total deaths. The assumption is made that the deaths occurring within 10 days of thermal injury are more likely to be related to the effects of shock or its treatment than are subsequent fatalities. The deaths from burns that occurred within 10 days of the injury were, in every instance, among persons who were given whole blood in the first 48 hours. That a balanced salt solution is adequate treatment for shock due to burns is attested to by the absence of mortality for 10 days after the burn in the group which received saline but no blood.

When all deaths are included and only the more severe burns are reviewed, as seen in table 2, the differences in total mortality are significant in the group with 30 to 44% of the body surface burned—27% mortality for those receiving blood as a part of therapy for shock and 4% mortality for those receiving only a balanced salt solution. The mortality difference for the group with more extensive burns (45 to 64% of the body surface burned) is highly significant. The 89% mortality for the blood-saline group compared to 36% mortality for the saline solution only group indicates that a balanced salt solution can be used effectively and safely in extensive burns as well as those involving limited areas of the body.

The same mortality differences for the two kinds of therapy for shock are found in table 3, when mortality is correlated with the depth of burn in addition to the extent of the burn. The burn index refers to all the third degree burns but takes into account only one-half of the area involved with second

From the Department of Surgery, The University of Texas, Southwestern Medical School.

TABLE 2.—*Parkland 1952-1956 Series Showing Mortality Between Groups According to Burn Area**

Burn Area, % Body Surface	Blood-Saline Burned, No.	Blood-Saline Died, No.	Saline Only Burned, No.	Saline Only Died, No.	Total Mortality, % Blood-Saline	Total Mortality, % Saline Only	p
30-44	11	3	28	1	27	4	0.03
45-64	9	8	14	5	89	36	0.006

* All deaths included; patients less than 61 years of age.

degree burns; thus, the index is weighted to reveal the effect of deep burns.

The correlation between high total death rates and early treatment with blood-saline may appear to reflect that, by chance, patients with lethal burns were selected to be treated with blood-saline. We do not think this is true; any difference in inherent severity of burns based on differences of area or depth that exist between the two therapeutic groups could not have influenced the results, because comparisons of mortality have been made between burns of similar size and depth. Some factors that may have influenced mortality other than the treatment variable have been reviewed; for example, the mean age of the patients is 26 years for the blood-saline group and 22 years for the saline solution only group. The frequency distribution of ages in the two groups is not widely discrepant: 33% of the patients treated with blood-saline and 41% of the saline only series were under 15 years of age; 9% of the blood-saline group and 6% of the saline solution only group were over 50 years old. The two series were not characterized by differences relative to the seasons of the year in which the burns occurred, to the time interval between injury and the beginning of treatment, or to the method by which the thermal injury was incurred (conflagration or scald). If some abstruse means of selection had been operative, the mortality expectancy of the Parkland blood-saline series should be inherently greater for burns of given extent than that found in other reported series.

TABLE 3.—*Parkland 1952-1956 Series Showing Mortality According to Depth and Extent of Burn**

Burn Index†	Mortality, % First 10 Days Blood-Saline	Mortality, % First 10 Days Saline Only	Mortality, % Total Blood-Saline	Mortality, % Total Saline Only	Patients, No. Blood-Saline	Patients, No. Saline Only
4-24	0	0	0	2	6	95
25-44	9	0	27	6	11	17
45-64	75	0	100	60	8	5
Total					25	117

* Tracheobronchial burns excluded; patients less than 61 years of age.
† All third degree + ½ second degree burn area.

The mortality expectancy can be derived by means of probit analysis which establishes a straight-line relationship between the size of the burn and the mortality. At various points along this line, one can determine the size of burn that is expected to be 10% fatal, 20% fatal, or 30, 40, 50, up to 100% fatal. The area of burn that is lethal in 50% of patients is arbitrarily used in comparisons of results to represent the entire series and is referred to as LA_{50}. This device obviates the complicated comparison of slopes of lines when evaluating the effectiveness of treatments used in different series.

In table 4, the LA_{50} of the 1952 to 1956 Parkland blood-saline treated series of burned patients does not differ significantly (p=0.3) from another series of burned patients treated with blood and saline that was previously reported[2] from Dallas, Texas, and Kankakee, Ill. The LA_{50} of the blood-saline series is nearly identical with that obtained in a combined series from Dallas, St. Louis, and Kankakee, in which several kinds of early treatment (plasma-saline, plasma-water, blood-saline) were used. The similarity of mortality expectancies is strong refutation of the hypothesis that the Parkland blood-saline series of patients was selected, and most likely this series did not include more fatally burned persons than would be expected to occur except by random. The relatively poor survival rate of the patients treated with blood and saline in Parkland Hospital as compared to the survival rate of those treated with a saline solution only is thought to be a function of the safety and efficacy of saline only. In corroboration, table 5 shows the mortality expectancies for the Parkland patients who were treated early with saline solution only and for combined series of patients to whom blood and saline solution were given. A higher rate of death expectancy was found in patients with all sizes of burns when blood-saline was used during the shock phase.

TABLE 4.—*Comparison of Lethal Area (LA_{50}) Among Three Series of Patients with Thermal Injury**

Therapy	LA_{50}†	
Blood-Saline, Parkland 1952-1956	48	
All Therapy,‡ Combined Series 1944-1952	49	p=0.3
Blood-Saline,‡ Dallas, Texas; Kankakee, Ill. 1944-1952	55	

* Patients less than 61 years of age.
† Derived from probits.
‡ Data reported by Moyer.[2]

Causes of Death: The deaths occurring in the first 10 days in the 1952 to 1956 Parkland series were all in the group which received blood in the first 48 hours, and these deaths were predominantly due to respiratory insufficiency. Postmortem examinations revealed a high incidence of pulmonary congestion, atelectasis, edema, and pneumonitis, as listed in table 6. The lungs were often heavy and noncrepitant. Since tracheobronchial burns are excluded, these findings are probably related to the effects of the peripheral burns or to the treatment.

As a result of these clinical observations, experiments were performed in our surgical laboratories to see whether burns which did not involve the tracheobronchial tree had any effect on respiratory function. It was found that deterioration in respiratory dynamics begins immediately after burning. In experimental scalds of 31 dogs produced by 30-second immersion of 40% of body surface in water heated to 85 C, Steph and colleagues[3] found a fall in total lung volume and a pronounced decrease in pulmonary compliance. The effects of different modalities of volume-replacement therapy were differentiated by giving one group of burned dogs lactated Ringer's injection (10% of body weight) and another group whole blood (3% of body weight). When lactated Ringer's injection (Hartmann's solution) was infused intravenously as treatment for the shock due to burn, the pulmonary compliance was found to improve, and, five hours after the burn, 60% of the animals had regained values of elastic compliance of the lung which exceeded those of the preburn state. When whole blood was given intravenously to combat shock due to burn, the compliance of the lungs continued to fall, and, five hours after the burn, 70% of the dogs were found to have a decreased compliance.

TABLE 5.—*Mortality Expectancy Derived from Probits**

Burn Area, % Body Surface	U.S. 1946-1951† Probit Y = 1.63+0.0592x‡	Parkland 1952-1956§ Probit Y = 1.71+0.050x
20	0.014	0.011
30	0.055	0.04
40	0.16	0.10
50	0.34	0.21
60	0.57	0.39

* Analysis includes all patients less than 61 years of age.
† Values for expected mortality (1.0 = 100%; 0.75 = 75%) in blood-saline series were computed by Moyer[2] and serve as reference for gross assessment of results achieved in Parkland Hospital by treatment of burns with buffered saline only during first two days after injury.
‡ % Body surface.
§ Saline only series.

Baxter and DeCosse[4] have demonstrated by pulmonary function and blood-gas studies (decreased arterial oxygen saturation with variable carbon dioxide pressure) in burned men that respiratory insufficiency begins early after burning and persists, often causing death several days later. All of their patients received colloid or whole blood treatment during the shock phase.

Use of Colloid Solutions: Some clinicians believe that colloid solutions, other than whole blood, are essential in treating burn shock. Rather than attack this thesis on theoretical considerations, a more valid refutation is presented in table 7, which compares the mortality expectancies of burned persons in whom shock is treated, with or without colloid. The mortality expectancies have been derived from probits, as recommended by Moyer,[2] so that the relative efficacy of different modalities of treatment used in one hospital may be assessed. All forms of treatment for shock were effective in patients with burns of 20 and 30% of the body, but patients with more extensive burns revealed wide discrepancies in mortality expectancy, depending on the form of therapy. For example, patients with burns that cover 60% of the body have 94% mortality expectancy when treated with normal human plasma but only 39% mortality expectancy when treated with saline solution only. The lowest mortality expectancy of the three groups occurred in the saline series for burns of every size, whereas the worst results were expected in the plasma series. The mortality of the Parkland saline series is compared in table 8 with the mortality that attended the use of colloid solutions in a combined series from St. Louis City Hospital; Homer G. Phillips Hospital, Dallas, Texas; and Kankakee Clinic, Kankakee, Ill. It is apparent that the omission of plasma or other colloid from the treatment of shock due to burns does not adversely affect survival rate.

TABLE 6.—*Parkland 1952-1956 Series Showing Causes of Death**

Cause	Early Deaths† Blood-Saline	Early Deaths† Saline Only	Late Deaths‡ Blood-Saline	Late Deaths‡ Saline Only
Pulmonary				
Bronchopneumonia	4	0	1	...
Congestive atelectasis	2	0	...	...
Pulmonary edema	6	0	...	...
Aspiration asphyxia	...	...	...	3
Renal				
Tubular necrosis	1	0	...	...
Septicemia	2	0	4	3
Enterocolitis	0	0	1	...

* Tracheobronchial burns excluded.
† Occurred within 10 days of burn.
‡ Occurred after 10 postburn days.

Although not routinely needed, normal human plasma may be used, with variable benefit in the management of two exceptional types of burned persons. One is the cachectic or malnourished person whose protein stores were depleted before the burn was incurred. This chronic starvation state may be associated with a poor hemodynamic and functional response to the infusion of quantities of salt solution which ordinarily effect recovery in other persons. Although this poor response to salt solutions usually portends a fatal outcome for the patient, the infusion of plasma has occasionally caused temporary improvement.

The other instance in which plasma may be used in burn shock is in management of the burned infant. Markley and colleagues[5] have reported that survival was improved in infants when plasma was used in a controlled clinical study conducted at Lima, Peru. Alternate, burned patients were given crystalloid solutions only, and no advantage to the use of plasma could be shown, except in infants.

TABLE 7.—*Parkland Mortality Expectancy Derived from Probits**

Burn Area, % Body Surface	1944-1947† Probit Y = 0.630 + 0.099x‡	1947-1951§ Probit Y = 1.683 + 0.067x	1952-1956‖ Probit Y = 1.71 + 0.050x
20	0.01	0.02	0.01
30	0.08	0.09	0.04
40	0.35	0.26	0.10
50	0.72	0.51	0.21
60	0.94	0.76	0.39

* 1.0 = 100% mortality.
† Plasma only; data from Moyer.[2]
‡ % Body surface.
§ Blood-saline; data from Moyer.[2]
‖ Saline only; all deaths included; patients less than 61 years of age.

TABLE 8.—*Mortality from Thermal Injury**

Burn Area, % Body Surface	U.S. 1944-1952† Burned, No.	U.S. 1944-1952† Died, No.	U.S. 1944-1952† Mortality, %	Parkland 1952-1956‡ Burned, No.	Parkland 1952-1956‡ Died, No.	Parkland 1952-1956‡ Mortality, %
15-24	127	2	2	65	1	2
25-34	66	5	8	17	1	6
35-44	47	12	28	23	0	0
45-54	20	10	50	7	1	14
55-64	25	20	80	7	4	57

* All deaths included; patients less than 61 years of age.
† Combined series of patients with burns who were reported by Moyer and were treated in St. Louis at St. Louis City Hospital and Homer G. Phillips Hospital; in Kankakee, Ill. at Kankakee Clinic; and in Dallas, Texas, at Parkland Hospital, 1944-1952; blood-saline-plasma series.
‡ Saline solution only.

Only plasma which has been stored for six months at room temperature should be used, for the limited benefits of plasma infusion do not warrant the great risk of homologous serum hepatitis that attends the use of fresh or lyophilized plasma. The use of dextran (Dextran, Expandex, Gentran) solutions in the treatment of burns is not necessary and probably not warranted, for experiments in our laboratory have revealed only detrimental effects attributable to dextran administered after burns.[6] Some improvement in length of survival of burned dogs could be shown when dextran was given in sodium chloride injection as opposed to no treatment at all. However, the use of saline solution alone gave a better survival record than the use of dextran in sodium chloride injection. The administration of dextran in water for injection was attended by poorer survival time than that shown by the group given no treatment.

Guides to Use of Electrolyte Solutions: We wish to establish (by the preceding discussion) that the essence of safe treatment for shock that attends burns is the replacement of the extracellular fluid losses. A balanced salt solution resembling the ionic composition of extracellular fluid can be given by mouth or by vein. Only 81 of 142 patients who were hospitalized for treatment of burns required intravenously administered supplements of the oral intake in order to control shock. Some patients with burns that involved up to 60% of body surface were effectively treated by oral ingestion of salt water only. The ingested solution contained 3 Gm. of sodium chloride with 1.5 Gm. of sodium bicarbonate per liter of water (Moyer's solution). The container was placed in a pan of ice at the patient's bedside, so the solution remained chilled. The volume of fluid consumed depended on the patient's wishes to drink. The management of the fluid losses after most thermal injuries is made easy, safe, and effective by simply offering the patient a weak salt solution to drink as desired. The only patients in our series who were denied oral ingestion were in peripheral vascular collapse, were vomiting, or had acute gastric dilatation.

To those patients who require intravenous replacement, the infusion of lactated Ringer's injection should be given as rapidly as necessary to overcome the symptoms of peripheral vascular collapse. The assessment of the circulatory status requires complete appraisal of the patient. Often the blood pressure cannot be measured by the sphygmomanometer because the extremities are burned. Even when the blood pressure can be recorded, it alone does not reliably indicate the presence of inadequate volume flow of blood; consequently, the functional alterations of the central nervous system, kidneys, heart, gastrointestinal tract, and sympathetic nervous system, as well as flow through visible peripheral vessels, are the indexes of inadequate circulation which must be used as guides to treatment. No formula of treatment can supplant observations of these functions of the patient. In order that trends can be seen, the observations must be made repeatedly. One looks for cool skin and pallor, with slowing of capillary return rates in unburned areas; empty peripheral veins, decreased arterial pulse volume, and increased pulse rate; diminished intensity of heart sounds, with a soft aortic second sound; excitement, thirst, restlessness, irritability, and disorientation, or sudden weakness, apathy, and decreased peripheral sensation; slowing of urine flow rates; and the

presence of nausea or vomiting. When these signs are present, additional water and salt replacement is needed, regardless of blood pressure level. When these signs are abolished by treatment, the rate of infusion can be slowed, even if blood pressure has not returned to normal.

The hemoglobin and hematocrit levels should not be used as primary guides to the volume of fluids required, because the symptoms of circulatory failure are often alleviated long before the hematocrit level returns to normal. If one persists in treatment in order to lower the hematocrit level, a dangerous fluid overload may be imposed.

In retrospect, the volumes of salt solution administered have varied predominantly with the size of the patient and the extent of his burn. By colligation of these factors, a rough relation can be derived; that is, for each 1% of body surface burned, 1% of the calculated extracellular fluid volume needs to be replaced. Burns involving 20% or less of the body surface usually do not require treatment of hypovolemia. The fluid deficits attending burns up to 35% of body surface are usually replaced adequately in the first day or two exclusively by the oral ingestion of the sodium chloride-bicarbonate solution. As an example of the fluid and electrolyte therapy required for a burn of 50% of the body surface in a man weighing 60 kg. (132 lb.), about three to four liters of lactated Ringer's injection may have to be given intravenously in the first 6 to 8 hours and another two to three liters within the next 16 to 18 hours. During this time, the burned person is permitted to drink a hypotonic salt solution. If large volumes of salt solution are consumed, the signs of fluid deficiency may be alleviated, and the intravenous requirements can be reciprocally reduced.

No plain water should be offered to the patient during this first day, for it will be taken in preference to the salty water. If large quantities of plain water are taken, the state of shock is not modified, and the retention of water that ensues causes a progressive dilution of the body's salt. The reduction in osmotic concentration is often attended by signs of increased intracranial pressure, and it may lead to frank water intoxication, with scanty urine flow. This state has been confused with burn "toxemia," but it can be specifically treated by the infusion of hypertonic sodium salts and withholding water.

If the burn is extensive and shock has been present during the first 24 hours, the oral ingestion of salt solution should be continued for another 24 hours. In those patients with extensive burns, some infusions of lactated Ringer's injection may also have to be given the second day. On the other hand, the patient with a burn of about one-third of his body surface or the patient with a burn that has not been associated with evidence of hypovolemia will probably not require the ingestion or infusion of salt solutions after 24 to 36 hours. When salt water is drunk exclusively for three days after a burn, a high serum sodium concentration develops, even though the solution drunk was hypotonic (0.45%). This electrolyte aberration is more likely to occur in hot weather in children and probably stems from the inability of the kidneys to concentrate salt in the urine and thereby to liberate sufficient plain water from the ingested saline solution. The insensible losses of plain water take place at accelerated rates through burned skin,[7] and more especially when the body temperature is elevated. When the serum osmotic concentration is elevated, the patient shows the signs of need for water, such as thirst, fever, dry mouth, small volumes of urine with high specific gravity, and perhaps disorientation. This state too is sometimes not clinically differentiated from burn "toxemia," but, when recognized, it can be definitively corrected by the administration of water.

When salt solution is administered at adequate rates and the signs of shock persist or recur, a frequent cause of the refractory shock has been found to be acute gastric dilatation. The distended stomach is sometimes visible as epigastric fullness, but nearly always gastric tympany can be percussed over a larger area than normal, and extending farther cephalad. These signs are attended by grunting respiration and effortless vomiting or nausea with epigastric discomfort. The treatment is to forbid any oral intake and to empty the stomach with a nasogastric tube. The reflex vascular collapse is relieved when the distended stomach is decompressed.

Another less frequent cause of shock refractory to volume replacement is hyperthermia. Body temperatures of 104 F (40 C) and above have been encountered in burned patients when compression dressings were used, especially in the summer. Hypotension and other signs of vascular collapse often attend the hyperpyrexia, but recovery from shock follows the reduction of body temperatures accomplished by immersion of the patient in ice packs.

Alleviation of Pain

Often the immediate concern in the treatment of a burned person is the alleviation of pain. Pain is adequately and promptly relieved by the intravenous injection of morphine sulfate or meperidine (Demerol) hydrochloride. Analgesia, not sedation, is the objective of medication, for signs of central nervous system dysfunction are valuable guides to the adequacy of treatment for shock and to detection of airway obstruction or other ventilatory defect. The amount given should be determined by the patient's response to a slow intravenous injection. Much less than the regular dosage of analgesic is required for pain relief in burns because the drug is given intravenously, because, the patient in shock is unduly sensitive to the effects of analgesics and depressants, and because the patient often experiences less pain from the burn than is anticipated. As determined by the patient's subjective response, 8 to 10 mg. of morphine sulfate administered intravenously often gives relief from pain. Much of the agitation and restlessness of the burned patient is interpreted as being due to pain, but actually it is behavior characteristic of the influence of anoxia. Commonly, the anoxia that occurs prior to treatment is incident to diminished cerebral blood flow, and the specific treatment of this apprehension is not morphine but rather fluid volume replacement and oxygen by mask. After the first few hours and when there is no evidence of circulatory insufficiency, the burned patient is ordinarily not in pain and not restless. Opiates can regularly be withdrawn at this time.

Measures Against Infection

Antibiotics are given parenterally for the first three or four days and then withdrawn until subsequent débridement is performed or until there is evidence of infection. Penicillin and streptomycin are commonly used for this initial period. The incidence of infection of the burned area has been little altered in our experience, despite frequent changes in our policy regarding the type, dose, route, and duration of antibiotic administration. Surface infection probably cannot be prevented by the use of systemic or topical antibiotics, but early systemic invasion by hemolytic organisms is effectively curtailed, as a rule, with penicillin given parenterally. The topical application of chemotherapeutic or antibiotic agents is futile in treating or preventing serious systemic infection, may be harmful by inducing sensitization, may allow the later emergence of antibiotic refractory organisms, causes maceration of the burned surface, and prevents dry eschar formation.

A tetanus toxoid booster dose should be given to patients who have been previously immunized against tetanus, and the opportunity to start active immunization should be taken in those who have not been previously immunized. Although active immunization will not prevent the development of tetanus early in the course of the burn, it may be of value in prevention of tetanus when repeated débridement and late reconstructive procedures are done. Passive immunization with antitoxin is not reliably effective in preventing tetanus with the usual 1,500 units, or even with 3,000 or 5,000 units. These and larger doses of antitoxin are attended by serum sickness, other severe allergic complications, and, occasionally, by anaphylaxis and death. The large doses with a high incidence of untoward reactions are not warranted unless the burn is excessively contaminated with material likely to contain Clostridium tetani.

Some recent immunological and experimental data suggest that treatment directed against a burn toxin may be

beneficial after thermal injury, despite repeated failures over many years to identify and isolate the toxin. Immune serum globulin and convalescent burn serum have properties which extend survival times when given to burned animals. The benefits of these substances and the question of freedom from dangerous reactions in the patient are not sufficiently established to warrant their use in burns in man.

Local Treatment

The local treatment of burns should be simple and free from ritual and should consist only of exposure to air. No immediate débridement is done, and no washing or scrubbing is done. Blisters are left intact unless they are large and obviously subject to early rupture; then they are aspirated with a fine needle. If gross contamination is present, the foreign particles are removed. The patient is then put in bed on sterile sheets, and a cradle is put over him. The cradle is covered with clean sheets. If the burn is confined to either the dorsal or the ventral surface, the patient is placed with the side of the burn upward. If the burn is circumferential, he is frequently turned, so the deep burns will form a dry eschar and the weeping areas will crust. The dry eschar of the burn is relatively impenetrable to bacteria as compared to macerated burned skin.[8] Soaks and topical applications are avoided.

Two complications of dry, contracted eschars must be promptly treated when they are recognized. Occlusion of the vessels of extremities may occur incident to the tightly constricting, leathery envelope of a deep circumferential burn of the arm or leg. The burned skin functions as a tourniquet. Ischemia of the digits and distal extremity may be recognized early by the presence of hypesthesia or by complete loss of light touch perception in unburned areas, even though pinprick may still be felt. The constrictive effect of the burn can be relieved by long linear incisions through the depth of eschar along the long axis of the extremity. The incisions can be made without anesthesia, since constricting eschars are produced by full-thickness burns which are insensitive. If edema of the muscles is severe, the deep fascia may also have to be incised over each muscle compartment. Ordinarily, however, incisions through the dermal burn only allow the subcutaneous tissues to protrude and relieve the tension.

When the chest or upper abdomen is circumferentially burned, severe respiratory restriction develops as a result of the inelastic girdle of burned skin. Respiratory excursions are shallow, tidal air is low, and carbon dioxide is retained. With severe restriction, the tidal air is little greater than the physiological dead space, and the burned patient becomes progressively asphyxiated. Death may occur in such instances by reason of the local effects of the burn, which, if incurred on another part of the body, would have been nonfatal. The garroting effect of circumferential chest burns can be relieved and lives can be saved if bilateral incisions are made vertically through the burned skin in the anterior axillary line. The incisions should extend down across the costal margin on to the abdominal wall, if the deep burn involves these areas. Immediately, the incised wound separates, and the liberated chest expands fully, with inspiration.

Treatment of Bronchopulmonary Complications

Tracheotomy is frequently required in the early management of burned patients with attendant respiratory problems. By means of clinical observations, autopsy findings, and experimental data, it has been shown that a respiratory defect, resulting in arterial desaturation associated with pulmonary congestion and decreased elasticity of the lungs, is a characteristic of thermal injury. If whole blood or colloid solutions are used to control shock, respiratory insufficiency may be exaggerated, and, occasionally, in patients with extensive burns (regardless of type of therapy for shock), the respiratory difficulty is progressive.

The first clinical evidences of these changes in the lung are delayed several hours and consist of an increased rate of breathing and tachycardia; then the expiratory phase of respiration becomes active and labored. Finally, inspiration is difficult, and interspace retraction can be seen; usually, by this time, there is gross evidence of arterial desaturation. Surprisingly, moist rales may not be heard, but usually auscultation of the lungs reveals an increased bronchial quality to the breath sounds, whereas vesicular breathing is absent in scattered areas. Sibilant rales are characteristically heard during expiratory effort.

Tracheotomy should be performed, and a cuffed tracheotomy tube should be employed in order to use intermittent positive-pressure breathing during the inspiratory phase. If this treatment is begun early, the changes in physical properties of the lungs may not be irreversible, and the congested state is alleviated along with an improvement in elastic compliance.

Another indication for early tracheotomy is for the treatment of burns of the upper respiratory passages. Mucosal burns on the tongue, mouth, or pharynx are evidence that tracheotomy will probably be required. If the patient is hoarse when first seen or becomes hoarse in the next few hours, tracheotomy should be performed immediately, in order to obviate more complete airway obstruction which nearly always follows hoarseness.

Tracheotomy is often necessary when the victim has inhaled noxious gases and smoke. There may be no signs of mucosal burn, but hoarseness is often present, coarse rhonchi and wheezes appear early, cough is frequent, inspiratory effort develops, moist rales and atelectatic areas occur, and frank pulmonary edema supervenes. These signs and their mode of progression serve to differentiate this laryngotracheobronchiolitis from the previously described pulmonary congestive state that may attend burns not directly affecting the respiratory passages. After performance of tracheostomy for burns of the respiratory passages or for inhalation of irritant gases, constant warm mainstream nebulization of water directly into the tracheotomy tube is necessary. These states are frequently fatal, but the use of anti-inflammatory steroids favorably modifies the pulmonary response to direct thermal injury. The addition of mucosal shrinking agents such as phenylephrine (Isophrin, Neo-Synephrine) hydrochloride to the nebulized water is beneficial in reducing frictional resistance to airflow. Intermittent positive-pressure breathing is usually required.

Another type of pulmonary injury, traumatic wet lung, is incurred with burns when explosion attends conflagration. Characteristically, there is an interval of many hours between the injury and the onset of cyanosis, with pulmonary edema. If one can anticipate the onset of this state from the history of explosion and by subtle evidences of pulmonary congestion, the performance of tracheotomy and the use of intermittent positive-pressure breathing can prevent death.

Miscellaneous Adjuncts to Treatment

The indications for use of gluco-corticoids (corticosteroids) in burns are probably limited to prevention of inflammatory response in the tracheobronchial tree after inhalation of smoke and other irritating gases and replacement therapy for those who have adrenocortical suppression as a result of previous steroid treatment.

Lowering of the body temperature has been suggested to have a favorable influence on severely burned persons, but we have been unable to demonstrate that over-all mortality is any different in hypothermic animals after a standardized scald than it is in normothermic controls. However, the hypothermic dogs lived longer.[9] Our preliminary experience with hypothermia in burned man indicates that it may be palliative but not definitively helpful.

Summary

The state of shock that attends thermal injury can usually be successfully and safely treated by balanced salt solutions given by mouth and vein. The use of whole blood and plasma in the first 48 hours after a burn is usually unnecessary and often harmful. Respiratory insufficiency commonly attends burns, and, usually, it requires the performance of a tracheotomy for adequate treatment. Incision of the eschar of a burn on the chest will, at times, relieve ventilatory in-

adequacy. Analgesics should be given intravenously in small doses and discontinued early in the course of the burn. The local treatment consists of exposure of the burn. Longitudinal incisions through the eschar of a burn on the extremities may be required to relieve the vascular occlusion incident to circumferential contraction of the burned skin. Antibiotics should be given systemically for three or four days after thermal injury, then withdrawn until specific indication for their need arises.

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COUNCIL ON DRUGS

Fluid Replacement in Shock and Hemorrhage

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► THE PURPOSE OF THIS PRESENTATION is to present briefly the fundamentals of resuscitation after injury or operation and to discuss, within this framework, the current frontiers of investigation and treatment.

After hemorrhage, the body's compensatory mechanisms are able to maintain a normal blood pressure until approximately 20% (1,000 cc.) of the blood volume has been lost. About this point the pressure begins to fall and by the time 40% (2,000 cc.) has been lost, the pressure becomes imperceptible. These estimates refer to acute hemorrhage. Chronic blood loss is much better tolerated, but acute blood loss, in the chronically ill patient whose blood volume is already contracted is tolerated poorly.

Agents Used in Replacement Therapy

The primary principle of replacement therapy is that the volume be replaced immediately in order to maintain the circulation and the exchange of oxygen and carbon dioxide as well as other essential substances. The preferable fluid is blood of the patient's own type, which is now available in almost every operating room in the United States. Since obtaining cross-matched blood requires time, it is not always available in the accident ward emergencies. What can be used while blood is being cross matched?

The experience in Korea demonstrated the feasibility and desirability of using type O blood containing a low titer of isoagglutinins. The blood was used without cross matching and without regard to Rh type. Thousands of units were administered, and the policy proved sound. Within moments of admission, a casualty could be receiving one or more transfusions. Civilian practice, with its problems of hemorrhage during obstetrical labor as well as in those patients who have previously been transfused, requires additional care as to Rh compatibility. It has proved quite feasible, however, to maintain in the emergency room and in the obstetrical and surgical suites two bottles of type O blood, low titer, Rh negative, for use in emergencies until cross matching has been achieved.

It cannot be overemphasized that blood is the preferable solution for replacement after hemorrhage. When blood is not available because of inadequate planning or unusual circumstances, compromises are essential. The volume of blood is more important than is the concentration of red blood cells. Normal human plasma is the most useful alternative, and it should always be available for instant use if type O blood is not on hand. The fact that there was a surplus of dried, inexpensive, conveniently available plasma left over from World War II spoiled the persons in charge of the blood banks. When the hepatitis virus made the use of this plasma impractical (plasma prepared from lots of 50 blood donors), the blood bankers tended to say that plasma was not good and, therefore, was unavailable. Plasma from single donors may be a bit troublesome to prepare, but its hepatitis risk is no greater than that of blood, and its shelf-life is much greater. On the basis of work by Allen[1] and others, which demonstrated that prolonged storage (six months) of plasma at room temperature would sterilize plasma of its hepatitis virus, the National Research Council has co-ordinated a national study of means of sterilizing plasma with heat. At present, these studies indicate that heating plasma to 60 C for 10 hours inactivates the hepatitis virus. The process, however, results in the loss of fibrinogen and in other changes in the plasma proteins. Nevertheless, studies at the time of this writing suggest that a useful modified plasma solution may result from this or from chemical sterilization.

A number of medical centers now recommend that immune serum globulin be administered to patients receiving multiple blood transfusions in an effort to prevent hepatitis. Statistical evaluation is not yet complete as to its efficacy, but, with an incidence of hepatitis carriers of 1 in 250 blood donors, such efforts seem well placed.

Concentrated normal human serum albumin (Albumisol, Normal Human Serum Albumin) remains available through the Red Cross, but it is not easily obtained because of its cost. However, it provides excellent expansion of the blood volume and, in the entire history of its use, only one patient has proved sensitive to the albumin. The latter record is unique since some patients with nephrosis have received hundreds of infusions of albumin.

Dextran (Dextran, Expandex, Gentran) in 6% sodium chloride injection has now been used for a decade as a plasma volume expander. It has proved useful, and few emergency rooms can function optimally over a prolonged period without dextran. Since its shelf-life is several years, a supply can be maintained in the emergency room with little difficulty and at modest cost. The national stockpile of dextran is now several million units.

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There is no arbitrary limit to the amount of plasma expanders which can be used. Their use always connotes a pressing need and a lack of the specific blood or plasma fraction. The amount to be given can only be titrated against this need. Experience indicates that the first one or two units administered are almost entirely safe and without danger of the development of any bleeding tendency in the patient.

When the aforementioned preparations are not available, sodium chloride injection should be administered, but its usefulness as a volume expander is limited.

Specific Problems

The problem which confronts the surgeon today is not what to give to replace blood volume deficiency; the problem is what to give after the blood volume has been restored. In most patients, no major problem persists. In a few, shock remains refractory or acute renal failure threatens. How can these problems be met?

First, how can we prevent acute renal failure? The only preventive method which has been found effective is to minimize the degree and duration of shock by restoring blood volume and, thereby, to restore the competence of the renal circulation. Neither hydration, diuretics, nor sympathetic nerve blockade have yet been demonstrated as being useful in preventing this dreadful complication. The metabolism of hemoglobin does not appear to be a causative factor, although transfusion reactions quite obviously result in a moderate degree of acute renal failure.

A number of studies have been reported recently pertaining to the treatment of refractory shock. Stirman and colleagues[2] have reported that, in dogs, sodium chloride injection lowers the mortality after replacement of blood. Others[3] have indicated that hydrocortisone (Cortef, Cortril, Hycortole, Hydrocortone) is of value, but this has not been confirmed in our laboratory, nor has it met our clinical need. Lillehei[4] has indicated that hydrocortisone and also autonomic blocking agents will lower the mortality in experimental shock due to bacteremia.

The role of vasoconstrictors remains controversial. From the laboratory, Webb[5] has currently reported the relative benefits derived when treating hemorrhagic shock in dogs. Lillehei failed to find any beneficial results from the use of vasoconstrictors in the treatment of septic shock.

In Korean experience and in civilian practice, the young man does not appear to benefit from vasoconstrictors. So far, in the resuscitation of thousands of injured young people, there has not been one whose life appeared to have been saved by vasoconstrictors. This does not seem to apply to the geriatric group. In the latter group, the coronary arteries and the cerebral arteries may be rather rigid and partially occluded by atheromatous plaques. Blood flow may be minimal, and a fall in blood pressure may prove catastrophic. A recent review[6] was made of those patients in our clinic who had suffered a cardiac infarction or a cerebrovascular accident during the 30 days after operation or injury. These patients were chiefly in the older groups. Nineteen patients had a myocardial infarction, 15 (79%) of which had occurred within the first week after operation. Half of these occurred on the day of operation or within 24 hours thereafter. Eleven patients had had cerebrovascular accidents, and these complications had their onset distributed equally throughout the first three weeks. Further review revealed that the patients with myocardial infarction had undergone varying periods of operative hypotension.

A similar clinical experience has resulted with acute renal failure, after resection of aortic aneurysms. For these reasons, vasoconstrictors, in conjunction with blood transfusions, may be indicated in the management of the older patients.

Finally, the blood pressure, refractory to multiple transfusions, may occasionally respond dramatically to the intravenous injection of 1 or 2 Gm. of calcium gluconate.[7] Presumably, this is due to an increased cardiac output which occurs as the concentration of ionized calcium is raised.

Summary

The treatment of shock after operation or injury consists primarily of restoration of blood volume with whole blood. Expedients and clinical evaluations of supplementary therapeutic measures may be superimposed, but the one fact remains paramount: The systemic ischemia and anoxia which result from traumatic shock is a major, continuing injury in itself. Every effort must be expended to prevent its occurrence, minimize its magnitude, and shorten its duration. The deleterious effects of this secondary insult are more disastrous than are the local effects of the primary injury.

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COUNCIL ON DRUGS

Emergency Care of Wounds

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► UNFORTUNATELY, wars have provided the greatest stimulus to advances in the treatment of wounds. Between wars, the basic principles of emergency treatment are frequently forgotten or are overlooked and have to be relearned at the expense of increased morbidity and mortality in the early phases of a new war.

Medical officials of the 15 North Atlantic Treaty Organization (NATO) nations recognized the need for documenting lessons of World War II and the Korean war. They, therefore, authorized the publication of a NATO handbook entitled, "Emergency War Surgery." It represents contributions of international experts who saw wounded soldiers at the front. The first draft was submitted to medical authorities of all 15 NATO nations as well as to 40 American surgeons with wartime experience, who generously offered criticism. The United States and Canadian issues have been released within the past year. Surgical principles contained in this volume are just as applicable at the local hospital as at the war front. With the prayer that this volume may never be required during war or mass casualties, I commend it to your use for the treatment of wounds encountered in peacetime.

Early Emergency Measures

Death of the patient within moments after a gunshot wound

is usually due to gross hemorrhage, to destruction of vital centers, or possibly to asphyxia. Even though the person appears to be dead, possibilities of resuscitation should not be overlooked. Clearing of the airway followed by artificial respiration with the mouth-to-mouth method, cardiac massage, or pressure transfusion by the arterial route might effect resuscitation in rare cases. If the patient is alive when first seen, certain surgical measures may have to be applied immediately, if he is to survive long enough for resuscitation and later necessary surgery. Foremost among the early measures are assurance of an adequate airway, the control of hemorrhage, if possible, and restoration of the circulating blood volume. Perhaps next in importance are occlusion of a sucking chest wound, release of tension pneumothorax, or the performance of a tracheostomy in impending asphyxia. If a patient survives the hazards of hemorrhage, asphyxia, or a serious cardiopulmonary imbalance, he then becomes a candidate for reparative or restorative surgical procedures. The patient's survival, beyond these measures, still is threatened by infection and by delayed physiological alterations. Among these late causes of death are delayed and so-called chronic shock due to the absorption of toxic products from necrotic tissue, which remains as a result of nonrecognition of devitalized tissues and inadequate débridement, severe electrolyte imbalance, and protein deficiencies. If these complications are to be held to a minimum, early resuscitation and surgical management must be in keeping with well-established surgical principles.

While resuscitation is being carried out, the surgeon should make a rapid appraisal of the extent of injuries and should determine which surgical procedures are of the highest priority. On occasion, in spite of the most heroic measures to overcome shock due to hemorrhage, failure of resuscitation may be due to continued bleeding within the chest, the abdomen, or other areas not controllable by tourniquet. Under these circumstances, the surgeon is forced to operate in an attempt to control the hemorrhage. The bleeding vessel should be secured through the most direct incision and with a minimum of trauma or other surgical procedures. Clamping of a large bleeding vessel will frequently result in a rapid improvement of the pulse and blood pressure, thus making resuscitation possible. Only after this has been accomplished may other indicated surgical procedures be carried out.

I can not emphasize too strongly the necessity for adequate refilling of the vascular tree, whether blood, plasma, or plasma expanders are used. Amounts must be given in such quantity as to restore systolic blood pressure to a minimum of 80 mm. Hg, preferably 100 mm. Hg before operation. During World War I, blood transfusions were rarely given. During World War II, the supply of blood was usually adequate on most fronts, and, on occasion, blood or plasma was given in large amounts. Not until the Korean war was it discovered that a single patient might require restoration of blood volume in amounts not only equal to his estimated blood volume before wounding, but, in some cases, in amounts even double or triple the estimated blood volume.

Estimation of Extent of Injury

In my opinion, the most important single factor in estimating the extent of damage due to gunshot wounds is knowledge of the type of weapon and the missile producing the wound. Although the size of the missile is of some importance, the velocity with which it is propelled is of the greatest importance. Stated in its simplest form, the amount of energy imparted to the body by a missile is derived from a formula in which the mass (the weight of the missile) is multiplied by the velocity squared. For example, before World War II, our military rifle fired a 30-caliber projectile at an estimated muzzle velocity of 2,300 foot-seconds (ft.-sec.). If all of the energy from this missile were transmitted to the tissues of the body, the estimate would be based on multiplication of the weight of the 30-caliber missile with the factor of 2,300 squared. Before the war, we had knowledge that the Japanese were developing a 25-caliber missile, which was projected at a muzzle velocity of 5,000 ft.-sec. It is immediately apparent that the weight of this missile is relatively unimportant when we consider multiplying that weight by the factor of 5,000 squared. Thus, the amount of energy imparted to the tissue determines to a great degree the amount of injury. On this basis, it is apparent that wounds produced by low-velocity weapons will cause little tissue damage remote from the track of the missile or weapon itself. For this reason, one of the simplest of wounds would be that produced by a knife or bayonet. Unless transection of a major vessel threatens life immediately, adequate inspection of the wound to its depth will disclose all of the injury present, and the surgical principles applied would be those dealing only with the local damage. Even high-velocity missiles, if fired from a great distance, may be practically spent when striking the body, and the amount of tissue damage may be minimal. This may be comparable to the amount of tissue damage produced by large or even small fragments, such as shell-casing fragments, if also projected a considerable distance. Such fragments, however, produce massive wounds and may produce tissue damage quite remote from the track, if the person is in close proximity to the explosion. Although the missile from a revolver may be equal to or larger in size than the average rifle missile, the velocity at the muzzle of a revolver is much less than that of the high-powered rifle. It is apparent, then, that the velocity of the missile and the proximity of the person to the wounding weapon become exceedingly important. Practically every conscious patient is able to describe the nature of the weapon, and the surgeon should anticipate the extent of tissue damage remote from the wound tract.

Importance of Adequate Débridement

In World War I, surgeons failed to recognize that tissue was damaged for many, many centimeters remote from a missile track. Wounds were inadequately débrided, in that devitalized tissue was not removed. Under these circumstances, primary closure of the wounds resulted inevitably in infection as well as the retention of necrosing tissue, which, because of its toxic effects, resulted in complications or death at a later time. This same principle applied when amputations were performed at or near the wound tract. Days after amputation, necrosis of tissue took place in the stump, and primary closure was out of the question. For this reason, the so-called guillotine amputation was the amputation of choice during World War I.

Even in the early days of World War II, débridement was woefully inadequate. Surgeons soon learned that boldness was essential and that the entire wound had to be exposed. Such an approach revealed, to a startling extent, the amount of devitalized tissue deep in the wound. In carrying out a débridement, devascularized skin should be excised, and all muscle that does not respond by contraction to pinching by a forcep should be removed. All viable bone should be left in place; in fact, large detached fragments of bone should be thoroughly cleansed and replaced in proximity to viable bone. Damaged nerves should not be débrided and should not be repaired at initial surgery. The site of nerve damage should be carefully described in the record, in order that later repair can be carried out.

Perhaps the most important surgical advance during the Korean war was the application of proper principles of débridement to major blood vessel damage. Surgeons trained at the Vascular Surgical Center, Walter Reed Hospital, were sent on special missions to the Korean front for the primary purpose of restoring the continuity of damaged major blood vessels in those wounded. In the first series of cases, in addition to excising all portions of a major blood vessel obviously damaged, the ends of the vessel (which appeared normal to the naked eye) were further resected. One centimeter of apparently normal vessel was removed from the proximal and the distal end of the resected vessel. Microscopic examination of these segments showed, in every instance, damage to the intima, which, inevitably, would have led to thrombosis and failure. This, then, explains the failure of attempts to repair or to bridge damaged major blood vessels among the casualties during World War II. Damage to major blood vessels in

the patients' extremities, both in World War I and World War II, resulted in an average amputation rate of 55%. At the Korean front, application of this single principle, together with the use of grafts to bridge wide gaps in a patient's major blood vessels, cut the amputation rate down to slightly less than 12%.

In carrying out débridement, after all devitalized tissue has been removed, care must be taken to cover denuded bone, nerve, or major blood vessels with muscle. This should be done, even if muscle groups need to be temporarily transposed to effect adequate coverage. Such wounds should never be closed primarily. The high rate of infection precludes such a procedure. After 7 to 10 days, secondary closure is performed. There are certain exceptions to this rule; for example, in the débridement of wounds of the skull, dura, or brain, the dura should be closed tightly, even if substitutes need to be used. The scalp and the skin on the face, because of a generous blood supply, may be closed primarily. It also is evident that wounds of the chest wall should be closed in order to prevent sucking. The abdominal wall should be closed tightly, except for drainage or exteriorization of large intestine, both being through separate incisions. In open wounds of the chest wall, one emergency procedure which has been valuable is the temporary closure with a series of towel clips, after which cleansing and indicated surgical measures might be instituted more leisurely.

General Principles of Wound Treatment

In addition to paying great attention to exploration of wounds to their depths, so that adequate débridement might be carried out, one should remember that missiles, especially those fired at high velocity, may travel great distances within the body. By following fascial planes, missiles entering the buttocks might ultimately lodge in the abdominal cavity or even traverse the diaphragm and produce damage within the chest. When a wound of exit exists, sighting along the line between the wounds of entrance and exit may give a rather faithful indication of the areas damaged, but the bizarre traverse of some wound missiles should lead one to suspect damage remote from the estimated missile track. This factor is especially important in that wounds of the abdomen or of the chest may involve both cavities.

In wounds of the neck, one must respect the multiplicity of organs and, therefore, be prepared to deal with injuries of the pharynx, trachea, or upper esophagus, as well as major blood vessels. It may be necessary to open the upper chest in order to secure great vessels of the neck at the points of origin. Care should be taken, wherever possible, to secure airtight closure of wounds of the trachea or esophagus. Even when this is possible, drainage must always be instituted. Tracheostomy should be performed if the surgeon suspects that it might be required. In other words, if a wound is such that one even considers the probability of tracheostomy, that alone is sufficient to warrant a tracheostomy. Even if the conditions present at the time of surgery would not seem to warrant tracheostomy, it is well to remember that later complications may demand it at a time when facilities may not permit an emergency procedure.

With reference to the hand, only that tissue which is obviously damaged beyond recovery should be removed. Every shred of tissue should be retained for future reparative surgery.

As a rule, wounds of the chest cavity, sufficient to lacerate or transect great vessels or chambers of the heart, result in death before the surgeon reaches the patient. It was well demonstrated during World War II that wounds of the chest should be treated conservatively. Sucking wounds, of course, should be closed and the possibility of tension pneumothorax should never be overlooked. Repeated aspirations of blood from the chest cavity usually suffice, though, on occasion, hemorrhage can be controlled only by thoracotomy.

Wounds of Solid Viscera

Wounds of the spleen, whether of the spleen itself or of the splenic pedicle, require splenectomy. In liver injury, detached or devitalized portions are removed. Whereas superficial lacerations may be sutured, deep lacerations require packing, especially to control hemorrhage. Adequate drainage must be established; drains should not be removed early, because collections of bile may become loculated. Injuries to the pancreas are serious. Lacerated or fragmented portions of the tail or body of the pancreas should be removed. Injuries to the head and the major ducts of the pancreas are usually fatal; even adequate drainage may not be effective in preventing widespread necrosis from pancreatic juices. As more experience was gained in World War II and in the Korean war, a more conservative approach was used in wounds of the kidney; control of hemorrhage, suture of the kidney substance, packing, where necessary, and routine drainage of the kidney area were effective in salvaging many kidneys of patients.

Wounds of Hollow Viscera

Throughout the length of the digestive tract, from the nasopharynx to the cecum, all wounds should be closed by primary suture. This may, of course, require resection of portions of the stomach and, especially, of the small intestine. It is to be remembered that small lacerations of the intestine should be closed transversely in order to avoid constricting the lumen. This principle in the surgery of the digestive tract, however, does not apply to wounds of the colon or rectum. Regardless of the procedure carried out, it must include a colostomy. In those portions of the large intestine where mobilization makes it possible, the damaged portion may be exteriorized in the form of a colostomy. Care must be taken, however, to assure that an adequate section of the colon is exteriorized in order that the colostomy may be a safe one. In transection of the large intestine, the two ends of the intestine may be brought out through the abdominal wall. A great portion of the large intestine, and especially of the lower sigmoid and rectum, can not be mobilized. Even though it may be possible in many instances to carry out a primary repair at the site of injury, a colostomy must be performed in an area of large intestine proximal to the site of injury.

Certain portions of the gastrointestinal tract do not lend themselves well to exploration. Therefore, care must be taken to discover wounds of the posterior wall of the stomach or of the second and third portions of the duodenum. In wounds of the ureter, the ureter may be primarily repaired, but diversion of the urinary stream proximal to the site of injury and repair should be carried out. This principle applies also to injuries of the urethra. Though it may be possible to repair the urethra over catheters or sounds, the temptation to leave an indwelling catheter alone should be avoided. In these instances, a cystostomy should be performed. When the bladder is injured, care must be taken to close that portion of the bladder which is within the peritoneal cavity, and a cystostomy should be performed through the extraperitoneal portion. Other hollow viscera or tubes include the gallbladder, which, if damaged, should be removed. Major biliary ducts should be repaired over, or bridged by, a long-armed T-tube. Again it is important that adequate drainage be established.

Hazards of Postoperative Period

When large quantities of blood or blood substitutes have been required to overcome shock due to hemorrhage and, especially, after major surgical procedures have been carried out after resuscitation, it is well to remember that such patients may later go into shock. Often the amount of blood volume restoration, which has been adequate to carry patients through operative procedures, will be found to be inadequate in the postoperative period. In practically all injuries, there is a certain degree of vasoconstriction. Filling of the vascular tree in the presence of vasoconstriction, whether it be produced through reflexes of the autonomic nervous system or by the use of vasoconstrictor drugs, may lead to a false sense of security. When vasoconstriction is released, the amount of blood within the vascular tree may be inadequate, and the patient will go into deep shock. This situation frequently evolves, and shock becomes present even

on such trivial movements as turning of the patient or transporting him from the litter to a bed.

Finally, one should never overlook the possibility of tetanus. Those patients who have been previously immunized against tetanus should have a booster shot. Those who have not had immunization should have protection by passive immunization during the period of recovery as well as later active immunization.

Comment

Over 31 years of my professional career were spent in the military service. A great amount of this time was spent in assisting surgeons from civilian life to perform surgery under military conditions. Included in this effort has been a major responsibility in the development of the NATO War Surgery Handbook. I can not leave the subject of the treatment of wounds without reminding all members of the medical profession of their grave responsibility in the case of war or, especially, of mass casualties. I personally believe that every physician should acquaint himself with at least the major principles delineated in the NATO document. He should be ready, willing, and able to participate in the care of mass casualties. The most experienced surgeon can contribute best in resuscitation, in appraisal of wounded, and in determining priorities of care. His supervision of less qualified surgeons will effect greater care to greater numbers. In the event of mass casualties, the nonsurgically trained physician, as well as the dentist and the veterinarian, should be utilized to care for burns, fractures, contusions, and lacerations, to débride soft tissue wounds, to control hemorrhage, and to perform resuscitation. Surgical procedures which require the training and abilities of the surgically trained specialists will require their services to such extent that the nonsurgically trained physician must be prepared to carry out all procedures short of major surgery within the abdomen, chest, neck, or head.

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The NATO handbook, "Emergency War Surgery" may be obtained for about $2.25 from the U. S. Government Printing Office, Washington, D. C.

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COUNCIL ON DRUGS

Management of Patient with Multiple Injuries

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► THE PATIENT WITH SEVERE multiple injuries offers one of the most challenging problems in medicine, but unfortunately the injured patient intrigues only a few physicians. The management of patients with severe injuries is not only difficult but has also become unpopular. Great emphasis has been placed on lowering the mortality after major elective procedures. It is almost impossible to obtain valid mortality figures on patients with multiple injuries. It is so easy to think that the patient, after serious trauma, has sustained so much injury that he cannot possibly live, and, therefore, the death of such a patient does not prey upon the physician's conscience as much as the loss of a patient who walks into the hospital requiring an elective procedure for a large gastric lesion.

The injured patient is usually not in the upper income bracket or the upper social strata and therefore is not so appealing to the private practitioner. All physicians are extremely interested in the prominent older citizen who has a prostatic difficulty, but few are interested in the rowdy youngster who is admitted, partially inebriated, in the middle of the night, with a gunshot wound or multiple injuries after an automobile accident. Most injured patients are admitted in the midst of a busy day or at night, and it has become common practice to shift the responsibility of the severely injured to younger physicians on the staff.

The emphasis on research and teaching in the fields of cancer and cardiovascular disease has aided considerably in improving the treatment of these entities. The field of trauma has received less emphasis. The treatment of the injured patient is an emergency and may become the responsibility of almost any physician.

It is the purpose of this communication to reemphasize well-established techniques in the care of the patient with multiple injuries and to outline a type of organization for care, along with an explanation of the physiological principles involved. Each patient with multiple injuries presents a different problem; therefore, it is impossible to suggest a specific routine for all patients.

Immediate Care and Transportation to a Hospital

For the extensively injured there are no rules that will cover all cases, but there are certain guiding principles. Unlike many single-injury states, multiple injuries require two specific aspects of care: (1) priority of certain systems for treatment and (2) organization of a team of persons to carry out therapy. Either at the scene of the accident or in the emergency room of the hospital, several professional and lay persons will make up the group that goes into action to care for the patient with multiple injuries. Irrespective of the level of care, someone must take charge. This person should be the one with the most advance experience and judgment. This leader is the most important factor in the organization of the care of the patient. He must assume full responsibility and dictate to the members of the team their specific tasks.

The first physician, whether he works at the scene of the accident, in a battalion aid station, in his office, or in an emergency room, carries a distinctive and heavy burden. He has the greatest opportunity to save life and limb. The physician who first sees the patient is not merely a first-aid man but an important member of the team who will resuscitate the casualty. The care that he gives is of an emergency type, but he must take time to institute procedures that will prepare the injured patient for transportation to the nearest hospital or for necessary surgical therapy. Hurried transportation to the hospital may lead to undue deterioration of the patient's condition during transportation. The importance of a short interval of time between injury and admission to the hospital is well recognized, but a slight delay for further restoration may be warranted because the patient may be better prepared to withstand the trauma of transportation. Emergency treatment at the scene of the accident should be the most complete care possible with the means available.

When an accident occurs and there are more than one injured, the patients must be sorted and cared for according to the urgency of their injury and the facilities available. The physician can usually tell with a quick glance the lifesaving measures that may be necessary immediately. The objectives of treatment should be, first, to stop the continuing insult of the wound and, second, to start restoration as soon as possible.

Maintenance of Adequate Respiratory Function.—The patient's airway must be kept open. Three to five minutes is about the limit before anoxia of the brain due to a plugged airway will produce permanent brain damage or death. Even if the obstruction is incomplete, the patient may not survive more than a few minutes unless the air passage is adequately opened. The patient should be placed on his side with the mouth open if he is unconscious. The operator's fingers may be covered with a handkerchief and used as a mouth gag. All foreign bodies should be removed, and the tongue should be pulled forward. It may be necessary to insert a safety pin

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through the tongue and attach it by a string to the clothing.

A sucking wound of the chest can be closed easily by a large bulky dressing. In some instances, it may be necessary to administer artificial respiration. Any one of several methods is useful. The operator should use the method with which he is most familiar. Mouth-to-mouth breathing is the simplest and very effective. The Holger-Neilsen procedure is familiar to many persons and is a highly effective method in providing adequate respiratory exchange. If a foreign body is lodged in the trachea, the patient may be encouraged to cough and expel it. After some injuries a tracheostomy is necessary.

Arrest of Hemorrhage.—After assurance of respiratory exchange, the next in priority is the arrest of hemorrhage. If hemorrhage is obvious externally, it usually can be stopped by the application of pressure directly over the bleeding area. Hemostats are convenient but usually are not necessary. The use of pressure points has been highly overemphasized, and it is doubtful if they are really of any value.

In general, tourniquets are to be condemned for use at the scene of the accident in almost all instances. It is rare that hemorrhage cannot be controlled by a well applied pressure dressing. In some unusual circumstances, however, it may be mandatory that a tourniquet be used to save life. If a tourniquet is utilized, it should be put on tight enough to occlude the arterial flow in the extremity. The most common difficulties with tourniquets are instability of the tourniquet causing loss of pressure, trauma to an underlying nerve, or compression insufficient to occlude arterial flow. If the tourniquet is applied with inadequate pressure or loosened after its application, it may occlude venous flow but not arterial flow and thereby cause greater loss of blood. When a tourniquet is applied, it should not be removed until the patient is in an institution and under the care of a physician who is prepared to deal with rapid major blood loss. Obviously, if the patient is bleeding from areas that cannot be controlled without an operative procedure, he should be transferred to the nearest hospital as rapidly as possible.

Preparation and Transportation to the Hospital.—It should be the initial physician's responsibility to put the patient in the best possible condition to withstand the further trauma of transportation to the hospital. After he has assured himself that there is adequate respiratory function and that hemorrhage has been arrested, other areas of injury should be attended. All fractures should be carefully splinted. If hypovolemia exists, an intravenous infusion of a plasma volume expander or an electrolyte solution should be administered during transportation to the hospital.

The importance of prompt admission to a hospital is well recognized, but preparation of the patient to withstand transportation may be more important. The commonest mistake in care, prior to a patient's admission to the hospital, are inadequate splinting, overdosage with morphine, inadequate control of hemorrhage, and transportation without proper preparation.

Great attention should be given to the patient's position. If he is unconscious, he should be placed on his side or on his abdomen with his head turned to the side. If there is any evidence of injury to the spine, the patient must be kept on a rigid support, such as a door, with his face down: when this is not available, he should be placed face down on a blanket so that the spine is maintained in slight hyperextension. If there is any question of cervical spine injury, traction on the head should be exerted by an attendant.

When a burn is associated with other injuries, it should be covered with a clean cloth and intravenous administration of fluids started.

Great care should be exercised in the use of narcotics initially. In some instances such as major fractures, burns, and abdominal injuries, it may be necessary to give an opiate; however, patients who are unconscious or who have a head injury, airway block, or severe shock should not be given a narcotic.

Initial Hospital Care and Resuscitation

Initial care in the hospital should be a simultaneous appraisal of the patient's condition and the institution of necessary resuscitative measures. One physician, preferably a general surgeon, should take charge and direct activities. While he is making a cursory examination and obtaining a few aspects of the history of the injuries, other physicians may be drafted to start work or assist in maintaining a good respiratory exchange.

History.—The initial history may be a short one, but a few questions to the family or to someone who has accompanied the patient may reveal important aspects concerning the mechanism of injury and pertinent aspects of the history of the patient. A description of how the accident occurred may lead the physician to suspect certain injuries and thereby be able to perform a better examination. The circumstances surrounding the accident may be revealing as to the organ systems that might possibly be involved in the injury. Sometimes, of course, the patient is able to relate a good history himself.

Physical Examination.—Initially, a rapid examination should be carried out. It must be a general one but follow an orderly plan. It may be necessary to cut off the clothes with scissors rather than traumatize the patient further by removing them. Examination should be directed first to the areas of obvious injury, but an over-all, quick examination also should be carried out. The following outline is helpful.

General: state of consciousness, respiration, pulse, position of patient, color, and odor.

Head: palpation of scalp and cranium, inspection of ears and nose for hemorrhage or cerebrospinal fluid, palpation of facial bones for fractures.

Eyes: state of the eyeballs and pupils. Not infrequently there is serious damage to the eyes in patients sustaining multiple injuries, and these are often overlooked. It should be of prime importance to obtain, as accurately as possible, the visual acuity of the patient. This should be recorded for each eye separately. Certain lifesaving procedures would receive higher priority, but early consultation with an ophthalmologist may permit him to carry out procedures that would be of considerable benefit in the prevention of loss of vision.

Mouth: inspection for foreign bodies, bleeding, or loose teeth.

Neck: state of blood vessels, inspection for internal or external bleeding, rigidity, possible injury to the cervical spine.

Thorax: observation of respiratory excursion, palpation of rib cage, heart action.

Abdomen: examination for distention, rigidity, observation of movement, and evidence of penetrating injury or tenderness.

Genitalia: examination for urinary extravasation, mechanical injury, or hematuria.

Extremities: palpation for tenderness, deformity, pulses, action of joints, color, temperature, sensation, and movement.

Skin: inspection for wounds of all types, including burns or irritations from gases or chemicals.

Roentgenograms.—In most patients with multiple injuries, certain roentgenographic examinations are necessary; however, such examinations are overemphasized. For the extensively injured patient, there is nothing rational in ordering roentgenograms of all bones which examination shows might possibly be fractured. One must decide whether a roentgenographic finding may change the treatment in the next few hours for the critically ill patient or whether he should be disturbed as little as possible. The patient should be subjected to as little further trauma as is absolutely necessary. Rapid changes in position usually lead to a fall in blood pressure in a hypovolemic patient.

It is not uncommon that many unnecessary roentgenograms of the skull are taken early. Unless the patient is cooperative enough to hold his head quietly, roentgenograms of the skull should be postponed unless the physician in charge believes they are absolutely necessary to determine the presence of an open depressed fracture or a fracture at a site which could readily produce injury to the middle meningeal artery. The necessary roentgenograms should be taken im-

mediately, but x-rays of questionable injuries should be postponed; however, the physician in charge should watch for the development of further symptoms and have the necessary films made later. An injury which at first seems apparently minor may give the patient the most trouble afterwards. This means that the management of the patient with multiple injuries is a continuing affair. The physician in charge must follow the patient until he has become stabilized after definitive care.

Records.—As soon as possible, the physician in charge should begin a record of the patient. This must include when the accident occurred, how it occurred, and where it occurred. The findings of the initial examination should be recorded, particularly the extent of vascular, nerve, and bone involvement, vision, blood pressure, and pulse rate. A sheet of paper pasted to the wall may serve as an excellent work form. As various resuscitative procedures are being carried out, running notes may be jotted on this sheet. This record can be of considerable value later in the course of management.

The medicolegal aspects of any injured patient are becoming increasingly more important. Good records are of considerable value in court. Frequently it is advisable to use color photographs to document the condition of the patient prior to treatment. These photographs should be kept in the physician's files and not released to legal counsel or the court unless the physician is present to interpret them.

Resuscitative Measures.—The physician in charge should designate a competent person to start resuscitative measures as soon as the patient is admitted. Usually a large needle is inserted into an accessible vein and blood drawn for cross matching. This needle is then used for the infusion of a plasma volume expander or an electrolyte solution. When hypovolemia exists, it can be minimized by the use of a plasma volume expander until whole blood is available. It may be necessary for the physician carrying out the resuscitative procedures to perform a tracheostomy or aspirate the chest. After severe injuries, and particularly after injuries about the pelvis, an indwelling catheter should be inserted in the bladder. This will give information as to the presence of hematuria and permit a more accurate record of the urinary output.

In some patients it may be necessary to do a cutdown on an accessible vein and insert a plastic catheter. This provides a good intravenous lifeline. The physician in charge should continue to watch bandaged areas to make sure that hemorrhage is adequately controlled.

In some patients it may be necessary to insert a gastric tube for evacuation of the stomach or as a diagnostic procedure to determine the presence of fresh blood in the stomach.

The patient's general systemic reaction to his wounds and to the resuscitative measures that are being carried out should be carefully observed. If hypotension continues, in spite of adequate fluid and blood replacement, other causes for the hypotensive state should be sought.

Preparation for Definitive Care.—In most instances, the physician in charge should be a general surgeon. He must consider the entire patient. No specialist can avoid being particularly interested in the problems of his own field. As soon as the physician in charge has completed his examination and has started resuscitative measures, he may want to call in consultants representing various specialty disciplines. These consultants should confer with the physician in charge, and a definitive plan of action should be outlined. The management should be defined in such a way that priorities for treatment are properly assigned.

In some hospitals, a roentgenographic diagnosis of a fracture automatically admits the patient to the orthopedic service. A fracture is about the only type of injury that will not kill the patient immediately. In fractures of the pelvis, the bony injury may never be lethal, but a rupture of the bladder or the urethra may result in death if unrecognized for a few hours. Fractures of the lower ribs on the left side frequently are accompanied by a rupture of the spleen or kidney. These are not orthopedic problems. With fractures of the upper ribs, the orthopedic surgeon would be the first to admit that his special training did not include the emergency handling of tension pneumothorax or paradoxical respiration.

Not infrequently, all unconscious patients are admitted to the neurosurgical service. This is an extremely dangerous situation, for the patient cannot communicate concerning pain and tenderness in various areas of the body. The percentage of craniocerebral injuries in which an immediate operation on the skull is indicated is extremely small, but if there is an abdominal injury on the same patient, timing of operation may be lifesaving. Again, the emphasis in care for the patient with multiple injuries is good organization and a physician in charge who keeps all anatomic and physiological areas in mind. After definitive care, certain specific injuries may become the major problem, and the responsibility for the patient can be turned over to whatever specialist is indicated.

Once all of the injuries have been diagnosed, it is necessary to decide which presents the greatest danger to life, which needs treatment first, and which can safely be ignored for the time being. No rule of thumb can be applied to the treatment of multiple injuries except that the lesions which offer the greatest danger to life should be dealt with first.

The restoration of cardiorespiratory physiology must come first, and then treatment of injury to the hollow viscera such as intestines, bladder, and occasionally lung and heart. Treatment of injuries of the liver, spleen, or diaphragm may accompany these procedures, if required. Open injuries of the muscle and bone receive next priority. Usually closed fractures, head injuries, and laceration of soft parts can wait until their care can be tolerated after the aforementioned injuries have been treated. Each treatment should be instituted at the earliest possible moment as decided by the physician in charge.

Definitive Management

As soon as the plan for definitive surgery is made, the patient should be put in the best possible condition for operation. It is most difficult to decide when a patient's blood volume has been increased to the extent that he can best tolerate anesthesia and operation. The value of adequate preparation for operation has frequently been emphasized in elective surgery. In the surgery of the injured man, it is even more important to prepare the patient by restoring his blood volume before operation. Unless continued hemorrhage is present and operation is mandatory to control this hemorrhage, the blood volume should be increased to near-normal levels by transfusion. Frequently, blood requirements may be judged by the size and character of the wound. The surgeon's guide to the adequacy of restorative treatment consists of general appearance of the patient, color of the conjunctiva, blood pressure level, pulse rate, and output of urine. If sufficient blood has been provided to permit good peripheral circulation, it will usually be indicated by the blood pressure. The adequacy of visceral blood flow can be estimated by the rate of urine flow. In the severely wounded patient, the output of 30 cc. or more of urine per hour suggests that the circulatory volume is approaching normal. The patient is usually ready for operation when the systolic blood pressure reaches 100 to 110 mm. Hg and his pulse rate falls to 120 per minute or less. In some instances, hemorrhage may occur as rapidly as blood is being replaced. In such cases, blood should be pumped through two or three veins and the patient should be placed on the operating table immediately. As soon as the hemorrhage is controlled at operation, further manipulation should be deferred until the blood volume deficiency has been restored.

Problems of anesthesia in relation to trauma are usually in direct proportion to the extent of injury. The best possible estimate of the condition of the patient will go far toward enabling the proper choice of anesthesia. The anesthesiologist should be consulted, along with other specialists involved, in the management of the patient and a general decision made with all of the facts at hand concerning the type of anesthesia best suited for the patient and the operative procedure. Occasionally, one may be confronted with an excessively de-

pressed patient as the result of overdose of a narcotic prior to transportation. Nalorphine (Nalline) hydrochloride may be a worthwhile drug to use in such circumstances. It antagonizes the respiratory and circulatory effect of the opiate. The selection of the anesthetic agent is rarely as important as is the person giving the anesthetic. The anesthesiologist should choose the type of anesthetic agent with which he is most familiar and is best suited to the over-all condition of the patient.

The surgeon may, with the help of his assistants, operate on one region of the body after another. In some instances, two surgical teams may operate simultaneously. For example, a patient suffering from an abdominal wound and a craniocerebral injury, accompanied by hemorrhage from the cranial wound, may be operated on first by the neurosurgeons, and then as a second procedure, a laparotomy can be carried out. If hemorrhage is occurring from both areas, two teams might operate simultaneously. It is not infrequent that two surgical teams operate on the abdomen and an extremity at the same time. The general condition of the patient and the further trauma of the operative procedure determine whether or not simultaneous operative procedures are warranted. In critically ill patients. the most-needed procedure is carried out first, and then, if the patient's condition permits, a further operation may be performed as a subsequent procedure.

The use of prophylactic tetanus immunization and early administration of antibiotics should always be considered. Wounds should be cleansed and properly débrided. Much loss of time and possible infection will be alleviated if wounds can be cared for early. One the other hand, soft tissue wounds usually do not endanger life, and their treatment further increases the hypovolemia. Since soft tissue wounds can be handled at any time, it may be necessary to apply a dressing and care for them later. When burns are associated with mechanical injury, the systemic effect of the burn should be corrected early by administration of appropriate fluids. As soon as the patient is prepared for operation, the mechanical injury can be treated. If fluid loss from the burn is being adequately replaced, the best time for the patient to withstand operative procedures is during the first few hours. After treatment has been given to the accompanying injury, local therapy of the burn wound can be accomplished, but this should receive lower priority.

Emotional stress as well as physical discomfort must be alleviated as much as possible. The physiological stress from the injury is usually a tremendous one, and it is the physician's responsibility to alleviate as much of the emotional stress as possible. If it is feasible, the physician should discuss the injuries with the patient and dispel any uncertainties that might have arisen in the patient's mind. Above all, the physician should pay particular attention to keeping the family appropriately informed. This helps to establish better rapport with the patient, gain his confidence, and is an important facet of the physician's art.

Summary

The patient with multiple injuries frequently receives inadequate treatment, because physicians are poorly informed and there is improper organization for the patient's care. The physician who first sees the patient with multiple injuries has a grave responsibility. He must arrest the continuing effects of the wounds and start restoration of the patient's condition. It is his responsibility to carry out the necessary resuscitative measures to prepare the patient to withstand the further trauma of transportation to the hospital.

In the hospital one physician should take charge. He should direct the over-all resuscitation and preparation for definitive care. Usually it is best if this physician is a general surgeon. He can call in the necessary specialists, but he must make the final decisions and assign priority of management. The secret to good definitive care is adequate preparation for operation. In the initial hospital management, there should be a careful appraisal of all injuries followed by adequate preparation for definitive operative procedures.

J.Am.Med.Assoc. 173:522 (June 4) 1960.

POSITIONS

in hospital pharmacy

PERSONNEL PLACEMENT SERVICE

The Personnel Placement Service is operated without charge for the benefit of hospitals and pharmacist members of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. The ultimate purpose is the improvement of pharmaceutical services in hospitals, by more adequately fulfilling hospital pharmacy personnel needs and by locating positions which provide challenging opportunities for pharmacists who have indicated an interest in a hospital career.

By participating in the service, the hospital indicates a desire to achieve a pharmaceutical service which meets the *Minimum Standard for Pharmacies in Hospitals.* A description of the position should be submitted to the Division of Hospital Pharmacy on the forms provided. The hospital will receive applications directly from the applicant. The hospital agrees to reply to each application received and to notify the Division of Hospital Pharmacy when the position is filled.

The pharmacist, by participating, agrees to submit a Personnel Placement Service Information Form to the Division of Hospital Pharmacy. The applicant will then be notified of openings listed with the Service as they become available and can negotiate directly with the hospital if he is interested. It is agreed that the Division of Hospital Pharmacy will be notified as soon as a position is accepted.

A listing of positions open and wanted will be made regularly in the AMERICAN JOURNAL OF HOSPITAL PHARMACY without charge. Neither the name of the hospital offering the position nor the name of the applicant will be listed, except by code. All inquiries should be directed as shown above, including the code number.

Address all inquiries to

Division of Hospital Pharmacy
2215 Constitution Avenue, N. W.
Washington, 7, D. C.

positions wanted

ASST. CHIEF OR CHIEF PHARMACIST—Female, married. B. S. obtained in 1954. Six years' hospital pharmacy experience. Prefers to locate in New York, New Mexico and Texas. Registered in New York, New Mexico, Texas and Louisiana. PW-282

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Ph.G. Degree obtained at Philadelphia College of Pharmacy and Science. Extensive hospital pharmacy experience. Prefers to locate in the North or West. Registered in Pennsylvania, Wisconsin, and Michigan. PW-281

STAFF OR ASST. CHIEF PHARMACIST—Male, married. M. S. degree obtained in 1958 at the State University of Iowa. Two years' hospital pharmacy experience. Served hospital pharmacy internship. Prefers to locate in California. Registered in New York. PW-280

CHIEF PHARMACIST—Male, married. Obtained B. S. in 1953 at St. John's College of Pharmacy. Seven years' hospital pharmacy experience. Prefers to locate in the Northeast. Registered in New York and New Jersey. PW-279

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. M. S. Degree obtained in September 1960 at Oregon State College. Hospital pharmacy experience. Served hospital pharmacy internship. Interested in a position with teaching duties. Prefers to locate in Ohio, Pennsylvania, or Indiana. Registered in Oregon, but will reciprocate. PW-278

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Received at Ohio State University B. S. Degree in Biology in 1952 and B. S. Degree in Pharmacy in 1955. Five years' hospital pharmacy experience. Willing to locate in the Eastern, Northern or Western part of the country. Registered in Ohio. PW-277

ASST. CHIEF OR CHIEF PHARMACIST—Female, single. B. S. obtained in 1956 at the University of Wyoming. Completion of work for M. S. Degree expected fall of 1960 at the University of Maryland. Served hospital pharmacy internship. Hospital pharmacy experience. Prefers to locate in the West. Registered in Wyoming. PW-276

STAFF OR ASST. CHIEF PHARMACIST—Female, married. B. S. obtained in 1954 at St. Louis College of Pharmacy. Six years' hospital pharmacy experience. Prefers the Northwestern part of the country, but willing to locate anywhere. Registered in Missouri. PW-275

CHIEF PHARMACIST—Male, married. Obtained M. S. in Hospital Pharmacy in 1954 at the University of Southern California. Served hospital pharmacy internship. Eight years' hospital pharmacy experience. Prefers to locate in the Northeastern part of the country. Registered in New York, New Jersey and California. PW-274

ASST. CHIEF OR CHIEF PHARMACIST—Male, single. Obtained M. S. in 1959 at the Medical College of Virginia. Served hospital pharmacy internship. Military obligation completed. Will be available for employment during September. Prefers to locate in the East. Registered in New Jersey. PW-273

CHIEF PHARMACIST—Male, married. Received B. S. Degree in 1957 at Purdue University. Two years' hospital pharmacy experience. Tour of duty in U. S. Army will be completed in September. Prefers to locate in the Southeastern part of country. Registered in Indiana and Illinois. PW-272

STAFF PHARMACIST—Male, married. Obtained B. S. in 1952 at Duquesne University. Prefers to locate in the Pittsburgh area. Registered in Pennsylvania. PW-271

ASST. CHIEF OR CHIEF PHARMACIST—Male, single. M. S. obtained in 1958 at the University of Texas. Served hospital pharmacy internship. Hospital pharmacy experience. Prefers to locate in the Southwest. Registered in Kansas and Texas. PW-270

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. obtained in 1955 at the University of Nebraska. Hospital pharmacy experience. Prefers to locate in the West or Midwest. Registered in Nebraska. PW-269

STAFF OR ASST. CHIEF PHARMACIST—Male, married. Ph.D. and B. S. obtained at the University of California. Two years' hospital pharmacy experience. Prefers to locate in California. Registered in California. PW-267

CHIEF PHARMACIST—Male, single. Obtained M. S. in 1954 at the University of Tennessee. Served hospital pharmacy internship. Six years' hospital pharmacy experience. Prefers to locate in the Southwest or in Florida. Registered in Connecticut and New York. PW-266

CHIEF PHARMACIST—Male, married. M. S. obtained in 1957 at the Nebraska University College of Pharmacy. Served hospital pharmacy internship. Six years' hospital pharmacy experience. Prefers to locate in the West or Midwest. Registered in Colorado, Missouri and Nebraska. PW-265

CHIEF PHARMACIST—Male, married. Obtained M. S. in Hospital Pharmacy at the State University of Iowa in June, 1959. Served

hospital pharmacy internship. Three years' hospital pharmacy experience. Will locate anywhere. Registered in Illinois. PW-264

CHIEF PHARMACIST—Male, married. B. S. Served hospital pharmacy internship. Extensive hospital pharmacy experience. Prefers to locate in the Midwest. Registered in Ohio. PW-263

STAFF PHARMACIST—Male, single. Obtained B. S. in 1957. Hospital pharmacy experience. Prefers to locate in the East. Registered in Texas and Washington, D.C. PW-261

CHIEF PHARMACIST—Male, married. B. S. Fourteen years' hospital pharmacy experience. Prefers to locate in the East or Midwest. Registered in Pennsylvania and West Virginia. PW-260

STAFF PHARMACIST—Female, single. Obtained B. S. in 1958 at West Virginia University College of Pharmacy. Served hospital pharmacy internship at Duke University Medical Center. Two years' hospital pharmacy experience. Prefers to locate in the Northeast. Registered in West Virginia and North Carolina. PW-259

CHIEF PHARMACIST—Male, married. Received B. S. at Temple University School of Pharmacy in 1938. Completed hospital pharmacy internship at Jefferson Medical College Hospital in 1960. Prefers to locate in East. Registered in Pennsylvania. PW-258

ASST. CHIEF PHARMACIST—Male, single. Obtained B. S. in 1956 at Purdue University. Hospital pharmacy experience. Prefers position with some administrative and/or teaching duties. Would like to locate in Northeast or Southwest section of country. Registered in Texas. PW-256

CHIEF PHARMACIST—Male, single. B. S. obtained in 1952 at the University of Illinois. Served hospital pharmacy internship. Two years' hospital pharmacy experience. Registered in Illinois. Prefers to locate in Arizona. PW-252

STAFF PHARMACIST—Male, single. Will obtain B. S. Degree at Oklahoma University. Prefers Oklahoma or surrounding states. Six months' hospital pharmacy experience. PW-250

CHIEF PHARMACIST—Male, single. Obtained Pharm. D. Degree in 1957 at the University of Southern California. Twelve years' hospital pharmacy experience. Registered in Minnesota and California. Prefers to locate in Minneapolis, Minnesota. PW-249

STAFF OR CHIEF PHARMACIST—Male, married. Obtained B. S. in 1959 at Medical College of South Carolina. Completed hospital pharmacy internship in June, 1960. Registered in South Carolina. Prefers to locate in Pennsylvania, Virginia or North Carolina. PW-248

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Obtained B. S. in 1954 at South Dakota College. Two years' hospital pharmacy experience. Will locate anywhere. Registered in South Dakota. PW-247

STAFF PHARMACIST—Male, married. Received B. S. in June, 1960, at Philadelphia College of Pharmacy and Science. One year's hospital pharmacy experience. Prefers to locate in Philadelphia. PW-246

STAFF OR ASST. CHIEF PHARMACIST—Applicant has held government position as Director of Medical Services in Sierra Leone, West Africa, since 1958. Holds B. S. Degree in Pharmacy from Drake University and has taken special courses in Parenteral Products and Radioisotops Techniques at Philadelphia College of Pharmacy. Served hospital pharmacy internship at University of Arkansas Medical Center. Additional hospital pharmacy experience in England. Registered in Iowa. PW-245

CHIEF PHARMACIST—Male, married. Obtained B. S. in 1953 at Ohio Northern University. Seven years' hospital pharmacy experience. Will locate anywhere. Registered in Ohio. PW-243

PHARMACIST—Male, single. Will obtain M. S. Degree in August 1960 at State University of Iowa. Four years' hospital experience. Prefers to locate in the New York City area. Registered in Iowa. PW-240

STAFF OR ASST. CHIEF PHARMACIST—Male, married. Obtained B. S. in 1950. Presently working for M. S. Degree at the University of Maryland. Two years' hospital pharmacy experience. Prefers to locate in the East. Registered in Maryland. PW-238

DIRECTOR OF PHARMACY SERVICES—Male, single. Received B. S. in 1956 at the University of California. Served hospital pharmacy internship. Four years' hospital pharmacy experience. Registered in California. Prefers to locate in California. PW-237

ASST. PHARMACIST—Male, single. Obtained B. S. at Xavier University in 1959. Will locate anywhere. Registered in Louisiana. PW-235

STAFF OR CHIEF PHARMACIST—Male, married. Obtained B. S. at St. Louis College of Pharmacy. Served hospital pharmacy internship. Three years' hospital pharmacy experience. Perfers to locate in Midwest. Registered in Missouri. PW-234

PHARMACIST—Male, married. B. S. received at Howard College of Pharmacy in 1956. Served hospital Pharmacy internship. Two years' hospital pharmacy experience. Prefers to locate in Florida. Registered in Florida and Alabama. PW-227

PHARMACIST—Female, single. M. S. received at the University of Maryland in 1951. Served hospital pharmacy internship. Five years' hospital pharmacy experience. Prefers to locate in New Jersey. Registered in Pennsylvania and Missouri. PW-225

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received at Detroit Institute of Technology in 1950. Four years' hospital pharmacy experience. Prefers to locate in Michigan. Registered in Michigan. PW-224

CHIEF PHARMACIST—Male, married. B. S. received at the University of Wisconsin in 1957. Four years' hospital pharmacy experience. Prefers to locate in Wisconsin. Registered in Wisconsin. PW-222

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Received B. S. at Medical College of South Carolina in 1950. Four years' hospital pharmacy experience. Prefers Southeast section of U. S. Registered in North Carolina and South Carolina. PW-221

CHIEF PHARMACIST—Male, single. B. S. received in 1952 at Massachusetts College of Pharmacy. Seven years' hospital pharmacy experience. Will locate anywhere. Registered in Massachusetts. PW-218

STAFF OR CHIEF PHARMACIST—Male, single. B. S. received in 1952 at St. Louis College of Pharmacy. Two years' hospital pharmacy experience. Registered in Missouri. Prefers to locate on the West Coast, particularly California. PW-217

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received in 1954 at the Southwestern State College in Oklahoma. Served hospital pharmacy internship. Three years' hospital pharmacy experience. Registered in Oklahoma. Prefers to locate in the Southwest. PW-214

STAFF PHARMACIST—Female, single. B. S. Seven years' hospital pharmacy experience. Southwest section of country preferred. Registered in Alabama and Georgia. PW-199

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. M. S. obtained in 1956 at Columbia University College of Pharmacy. Hospital Experience. Prefers to locate in California. Registered in New York, Michigan, New Jersey and Florida. PW-184

ASST. CHIEF OR CHIEF PHARMACIST—Male. B. S. received in 1954. Desires to locate in Michigan, Ohio or Illinois. Registered in Michigan. PW-177

PHARMACIST—Female. Graduate of the University of Idaho, 1954. Registered in Illinois. Hospital experience. Prefers Chicago area. PW-166

ASST. CHIEF OR CHIEF PHARMACIST—Female. B. S. and M. S. Purdue University. Ten years' hospital pharmacy experience. Registered in Indiana and Kentucky. PW-164

ASST. CHIEF PHARMACIST—Male, single. Registered in N. Y. and Vt. Served hospital pharmacy internship, now employed part-time staff pharmacist. Prefers Eastern part of country. Has M. S., four years' hospital pharmacy experience. PW-154

CHIEF PHARMACIST—Male, married. B. S. Ten years' hospital pharmacy experience. Registered in Mass., Ill., Mo., Ky., Tenn., and Va. PW-150

PHARMACIST—Male, single. B. S. received in 1959. Prefers to locate in East. PW-149

ASST. CHIEF OR CHIEF PHARMACIST—Single, male. Registered in D. C., Ill., Md., and Pa. Graduate University of Pittsburgh in 1953, experience in research. Prefers North and East. PW-148

CHIEF PHARMACIST—Male, married. Graduate of St. John's University College of Pharmacy. Extensive experience as chief pharmacist and purchasing agent. Prefers to locate in New York or New Jersey. Registered in New York and New Jersey. PW-144

ASST. DIRECTOR OR DIRECTOR OF PHARMACY SERVICES—Male, single. B. S. Retail and five years' hospital experience. Registered in Illinois. PW-119

CHIEF PHARMACIST—Female, single. Registered in Pennsylvania and Ohio. Twelve years' hospital pharmacy experience as a chief pharmacist. Desires to locate in Pennsylvania or Ohio. PW-111

positions open

CHIEF PHARMACIST—100 bed general hospital located in Ohio. Applicant must have organizational ability and will assume administrative responsibilities of the dept. Must be registered. PO-224

ASST. CHIEF PHARMACIST—90 bed general hospital located in

Colorado. Duties include compounding and dispensing medications and assuming responsibility of pharmacy dept. in chief pharmacist's absence. Must be eligible for licensure in Colorado. Forty hour week, vacation, sick leave and hospitalization. PO-223

STAFF PHARMACISTS—400 bed general medical, surgical and teaching hospital. Duties include inpatient and outpatient dispensing, manufacturing bulk liquids, ointments, galenicals, small and large volume parenterals and surgical fluids. Will also assist in supervision of students and hospital pharmacy interns. Prefers applicant with hospital pharmacy experience and/or hospital pharmacy internship, with some manufacturing experience. Male preferred under forty years of age. Forty hour week, vacation and educational benefits. PO-222

CHIEF PHARMACISTS—Psychiatric hospital located in Ohio. Must be registered in Ohio, forty hour week, vacation and retirement benefits. PO-221

ASST. CHIEF PHARMACISTS—12,000 bed neuropsychiatric hospital. Duties include filling prescriptions and ward drug orders, advising and assisting non-professional pharmacy personnel and maintaining alcohol and narcotics records. Licensure in Georgia required. Forty-four hour week, vacation, sick leave, and retirement. PO-220

STAFF PHARMACIST—400 bed general hospital located in Texas. Duties include dispensing, etc. Applicant must have B. S. and be eligible for registration in Texas. Forty hour week, two weeks vacation. Write: Pharmacy Department, Harris Hospital, Fort Worth, Texas. PO-219

ASST. CHIEF PHARMACIST—200 bed general hospital located in Connecticut. Duties include filling of medication orders, preparing stock drugs and filling inpatient and outpatient prescriptions. Forty hour week, two weeks vacation and sick leave. PO-218

CHIEF PHARMACIST—260 bed general hospital located in Oklahoma. Duties include planning and organizing policies of dept., preparing and dispensing medications. Prefer applicant with supervisory experience between 25 - 40 years of age. Forty hour week, vacation, sick days, group hospitalization and pension program. PO-217

ASST. CHIEF PHARMACIST—400 bed hospital. Duties include supervision of general dispensing pharmacy. Prefers applicant who has served an internship. Ohio registration required. Forty hour week, vacation, retirement program and educational opportunities. PO-216

STAFF PHARMACIST—350 bed general hospital. Duties will chiefly consist of dispensing and some manufacturing. Possibility of teaching pharmacology subjects to student nurses. Qualifications: Male, 25 - 30 years of age, service obligation completed B. S. and Ohio registration. Vacation, holidays and sick leave. PO-215

STAFF PHARMACIST—188 bed general hospital. Duties include filling patient drug orders and outpatient prescriptions, and assisting chief pharmacist. California registration desired. Forty to forty-eight hour week, vacation, sick leave and group insurance. PO-214

ASST. CHIEF PHARMACIST—380 bed general hospital located in Colorado. Duties include compounding, dispensing, maintaining stock of pharmaceuticals, and furnishing information concerning medications to physicians, interns, and nurses. Responsible for operation of pharmacy department in absence of chief pharmacist. Vacation, holidays and sick leave. PO-213

CHIEF PHARMACIST—190 bed community hospital located in Virgina. Applicant must have administrative ability as well as organization ability. Must be interested in teaching. Close relationship with medical and nursing staff of the hospital. Forty hour week, vacation, sick leave and retirement plan. PO-211

ASST. CHIEF PHARMACIST—220 bed general hospital. Will be in charge of pharmacy in chief pharmacist's absence. Qualifications: female, B. S., experience in pharmacy administration, licensed in Pennsylvania. Forty hour week, vacation, progressive personnel policy. PO-209

ASST. CHIEF PHARMACIST—500 bed general childrens hospital located in Iowa. Will assist chief pharmacist and will be responsible for the operation of the pharmacy dept. in the absence of the chief pharmacist. Forty hour week, vacation, sick leave and holidays. PO-205

ASST. CHIEF PHARMACIST—238 bed general hospital located in Michigan. Duties include dispensing, controlling pharmacy divisions on nursing units, and assuming responsibility of pharmacy in the absence of chief pharmacist. Forty hour week, vacation, holidays, and sick leave. PO-204

ASST. CHIEF PHARMACIST—204 bed hospital. Duties include dispensing, receiving, and labeling drugs, etc.; furnishing information to physicians and nurses; teaching student nurses; and being responsible as an assistant department head in administrative and other related duties. Forty hour week, vacation, insurance, and sick leave. Must be eligible for registration in Illinois. PO-203

CHIEF PHARMACIST—104 bed general hospital. Direct pharmacy with the help of full-time registered nurses and assist in the purchase of medical surgical supplies. Forty hour week, vacation, and sick leave. Located in a university town in Illinois. PO-202

STAFF PHARMACIST—280 bed general hospital. Intern and resident program, school of nursing and school of medical technology. Building program to include new pharmacy facilities. Must have B. S. in Pharmacy. Michigan registration required or be eligible for licensure. Recent graduate acceptable. Forty hour week, vacation, insurance, pension plan, holidays, and sick leave. PO-199

CHIEF PHARMACIST—300 bed hospital located in Virginia. Pharmacist will have responsibility of organizing dept., purchasing initial stocks, planning policies and procedures, establishing formulary, and serving on Pharmacy and Therapeutics Committee. Forty hour week, vacation, and sick leave. PO-195

STAFF PHARMACIST—790 bed hospital. Duties include handling and filling of inpatient and outpatient departmental orders, outpatient prescriptions and bulk manufacturing. Must be registered or eligible for registration in Ohio. Male preferred. Forty hour week, vacation, holidays, and pension plan. PO-194

ASST. CHIEF PHARMACIST—225 bed general hospital in Hawaii. Assist chief pharmacist; charge of dept. in chief pharmacist's absence. Must be eligible for licensure in Hawaii. Forty hour week, vacation, holidays, annual sick leave, insurance and retirement plans. PO-191

CHIEF PHARMACIST—2300 bed mental hospital. Pharmacist will have complete charge of pharmacy, drug orders, stocking, dispensing, compounding, necessary records, and other pharmacy duties. Must be licensed in Ohio. Forty hour week, vacation, holidays, insurance, retirement plan, and sick leave benefits. PO-189

STAFF PHARMACIST—325 bed general hospital located in Pennsylvania. Duties include filling requisitions from the various nursing stations for floor drugs and completing specific prescriptions to patients. Forty hour week, vacation, and group hospitalization. PO-186

STAFF PHARMACIST—400 bed general hospital located in Michigan. Excellent opportunity in an expanding pharmacy program. Liberal benefits. PO-185

CHIEF PHARMACIST—312 bed nonprofit community hospital. Male or female. Must be qualified and eligible for licensure in Virginia. Forty to forty-four hour week, vacation, and insurance plans. PO-181

CHIEF PHARMACIST—264 bed general hospital located in Texas. Plans and directs pharmacy policies, compounds and dispenses medicines, purchases supplies and materials, maintains records, and prepares periodical reports. Must be eligible for or have M. S. Degree. Forty hour week, vacation, retirement, sick leave and insurance plans. PO-177

STAFF PHARMACIST—290 bed general medical and surgical city hospital. Duties include compounding dispensing, manufacturing, and assisting in the purchasing of supplies. Prepares reports and maintains records. Furnishes information concerning medications to physicians and nurses. In absence of associate pharmacist will assist with special duties as assigned by chief pharmacist. Male or female between 23 - 45 years of age. Ohio registration required. Hospital pharmacy internship preferable. Forty hour week, vacation, sick leave, retirement plan, credit union, holidays, and insurance. PO-170

STAFF PHARMACIST—200 bed general hospital. Duties include compounding, dispensing, and manufacturing. Applicant must have B. S. in Pharmacy and be registered in Connecticut. Recent graduate acceptable. Forty-four hour week, vacation, pension plan, and hospitalization. PO-168

STAFF PHARMACIST—100 bed general hospital located in Texas. Assume personal responsibility for accurate filling of prescriptions and supplies, assist in inspecting drugs in nursing stations, replace stock taken from night emergency container, inspect and refill ophthalmic solution trays from operating room, emergency room, and central supply. Female preferred. Must be registered or eligible for registration in Texas. Forty hour week, vacation, holidays, and sick leave. PO-164

ASST. CHIEF PHARMACIST—280 bed general hospital. Duties include filling prescriptions and medication orders from various units, supervise pharmacy clerks, assume administrative responsibility when chief pharmacist is absent. Forty-four hour week, sick leave, and holidays. Must be registered in Illinois. PO-161

CHIEF PHARMACIST—103 bed general hospital. Purchasing, receiving and issuing of pharmacy supplies. Taking inventory once a year. Filling out various reports necessary to operation of dept., etc. Must be registered in Washington State. Forty hour week, vacation, holidays, sick leave, and insurance. PO-158

STAFF PHARMACISTS—Unique, new 400 bed general private hospital where pharmacists join the doctor-nurse team by working in a dispensing unit location on each 100 bed nursing unit or in the central pharmacy. The dispensing unit personnel have responsibility for providing drugs, oxygen, dressing trays, I.V. solutions and similar items. A total of sixteen staff pharmacists is required to staff the hospital. Applicants must be eligible for registration in California. Excellent opportunity; generous benefits. PO-148

STAFF OR ASST. CHIEF PHARMACIST—150 bed general hospital located in New Mexico. Generous benefits. PO-134

STAFF PHARMACIST—500 bed general hospital located in Oklahoma. B. S. required. Forty hour week. PO-95

ASST. CHIEF PHARMACIST—237 bed general hospital in West Virginia. Female desired. Forty-four hour week, vacation. PO-77

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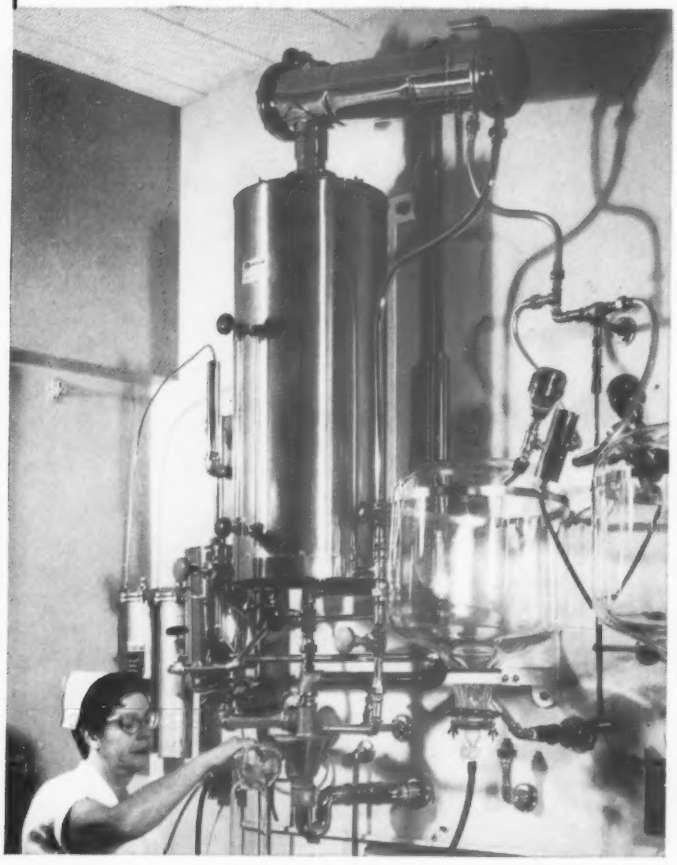

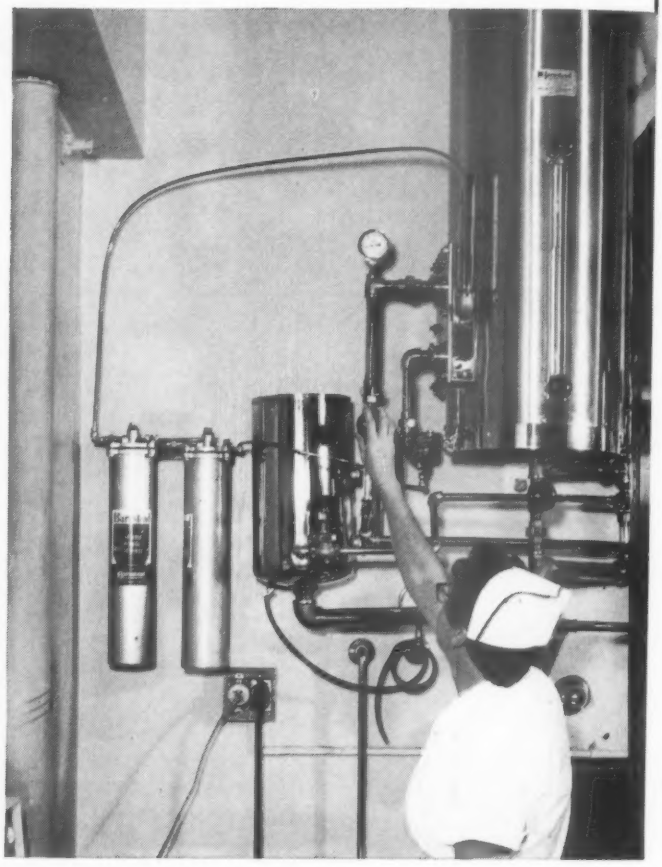

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